Foreword to Introduction to Clinical Reasoning

Thank you for your interest in clinical reasoning, one of the most important, yet also most challenging, skills for medical practitioners to master. In the subsequent pages, we provide an example curriculum for teaching clinical reasoning to pre-clerkship medical students, which we have iteratively developed over many years of working with both students, as well as faculty members, from diverse medical specialties. This curriculum also may prove to have considerable value for students on their clinical rotations, and even beyond that, as medicine, perhaps more than any other field, is characterized by lifelong learning.

At our institution, the Introduction to Clinical Reasoning (ICR) curriculum has undergone marked modification in recent years as we have morphed our “traditional” 2-year preclinical medical school curriculum into a new 18-month, organ system based pre-clerkship curriculum, across which ICR is longitudinally woven. This curriculum significantly impacts how our topics are sequenced.

We attempted to follow instructional design principles, moving from straightforward to atypical to complex presentations both by the topic sequencing as well as the small group cases within each topic. In the initial topics, we provide a lot of guidance for students, but over time, we ask them to take more responsibility and demonstrate greater independence in clinical reasoning thus preparing them for the clinical clerkships.

Our instructional techniques are based on a variety of theoretical lenses and current “best practices” in clinical reasoning (see introduction). The curriculum addresses a variety of common symptoms, physical findings, laboratory abnormalities and syndromes (the synthesis step just proximal to the diagnosis, e.g. nephritic syndrome or exudative pleural effusion). This is done intentionally to give the learner exposure to the variable degrees of problem resolution that they will encounter in clinical practice. We also attempt to integrate common tools and methods that the expert physician uses when approaching the topic so that the learner gleans both valuable content and strategies for approaching clinical reasoning.

At our institution, each introduction to clinical reasoning topic includes a small group instructional session. In our case-based instruction, experts facilitate small groups of 5-7 students and each learner evinces clinical reasoning during these active case-discussions employing the clinical information provided in the syllabus topic. We attempt to optimize student-facilitator ratio to allow each learner to demonstrate his or her clinical reasoning and receive expert level feedback at an appropriate level. Additionally, we provide a synthetic post-exercise topic wrap-up large-scale lecture that encourages student-derived questions to solidify learning on the topic.

We also provide a number of enhancements within each topic. These include a number of worked examples, or sample cases, with questions posed that are addressed at the end of each topic. Each topic also includes a number of practice questions, with accompanying answers.
There are several more novel approaches, such as script concordance testing and a clinical integrative puzzle (see pleural effusion topic). Additionally, we have developed some concept mapping exercises on ICR topics in conjunction with our department of pathology that we would be happy to share with faculty readers of this book, upon request. Further, we integrate pediatrics and psychiatry into pertinent topics so that the learner is given a broad approach to each topic in the syllabus.

Finally, we are indebted to our faculty authors who not only have written the topics (chapters) before you but also lead in the selection of expert clinical teachers and assist in the ongoing, iterative development and refinement of instructional strategies used in each topic session. This includes studying clinical reasoning in our pre-clerkship learner population on topics such as authenticity of instruction, motivation and emotion, and clinical reasoning performance from a variety of theoretical and methodological stances. We would be happy to provide references upon request. For several topics the small group activity involves seeing live standardized patients who have been provided with scripts instructed in proper presentation, at our Simulation Center, rather than simply working through “paper cases”, and we can convey details about how we did this for the benefit of faculty at other institutions.

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INTRODUCTION TO CLINICAL REASONING
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Objectives:
At the end of this session, students will be able to:
1. List different strategies that physicians use to solve clinical problems
2. Describe how to construct a problem list
3. Define sensitivity and specificity
4. Calculate positive and negative predictive values

Introduction
Welcome! The foundation of clinical medicine is the ability to obtain, understand, and act upon symptoms and observations (the clinical “data”). This ability to synthesize clinical “data” requires both the acquisition of factual knowledge and experience. To be effective, the multiple fields of literature show that experience must be deliberate (deliberate practice, Ericsson, 2006). Deliberate practice argues that expert performance is acquired gradually through effortful, relevant concentration on improving specific skills (typically under the guidance of a teacher or coach). This course will provide you with deliberate practice in clinical reasoning through a sequence of lectures and small group discussions of germane topics in medicine with the help of a cadre of inter-departmental physicians. Clinical reasoning—the process of translating presenting history, physical, laboratory and radiographic data into a problem list, differential diagnosis and treatment plan—is often referred to as the “bread and butter” of clinical practice (Richardson, 2007). We believe this course is essential for helping you succeed in the clerkship years.

There is little doubt that learning medical facts is an essential determinant of expert performance in medical practice. Yet, scientific principles and medical facts represent only one aspect of the cognitive demands on the physician. Another demanding aspect is solving clinical problems including coherently synthesizing a patient's presenting clinical symptoms and findings, proposing a set of diagnostic hypotheses (a differential diagnosis), selecting tests to confirm or refute these hypotheses, and making decisions that encompass the trade-offs between the risks and benefits of tests and treatments.

The Introduction to Clinical Reasoning (ICR) Course is not meant to be a comprehensive overview or outline of your clerkship years. The clinical skills sequence teaches you how to acquire clinical information (the history and physical). ICR will teach you how to use the knowledge you are acquiring to arrive at a problem list and differential diagnosis as well as how establish the diagnosis and a basic treatment plan—we will introduce you to several ways how physicians approach solving clinical problems.

This course will demonstrate how to use scientific knowledge in handling clinical problems to make you a thinking clinical scientist rather than a practitioner who uses facts by rote but doesn't understand the reasoning involved. You should learn which information to seek
and what to do with it when you have it. This is a course in problem solving that is meant to help you excel on the clerkships.

**Course Goals and Format**

The purpose of this course is to introduce you to the process of clinical reasoning. This course will help facilitate the transition from **Reporter** to **Interpreter**. Like a newspaper reporter, a **Reporter** can collect and convey the patient’s “story” in both written and oral formats without significant omissions or digressions. **Interpreters** are able to “translate” the patient’s “story” into a problem list and differential diagnosis that they can defend with history, physical exam, and ancillary test facts (i.e. laboratories and radiographs). Reporters can complete to “S and O” of the SOAP note, Interpreters can complete the “A” (assessment or analysis).

This course is arranged as a series of topics--symptoms, physical exam findings, laboratory test abnormalities, and syndromes (see syllabus schedule). **Syndromes** are symptom complexes at the step just prior to the diagnosis such as kidney failure or thyrotoxicosis. In the small groups, you will work through “cases” for common and/or serious presenting diagnoses for each topic and you will be asked to synthesize presenting symptoms and findings into a problem list, differential diagnosis, and at times the “next steps” in the diagnosis and/or treatment using proper medical terminology (or **semantic competence**).

You will learn **Reporting** skills in the **clinical skills courses**; ICR reinforces these reporting skills through helping you further characterize presenting symptoms (with clinical skills courses) and recognizing the interpretation of pertinent physical examination data (with clinical skills courses). We will stress the recognition of key symptoms and findings from the cases to help you synthesize a problem lists, differential diagnoses, and next steps taken to establish the diagnoses. *We will also point out the common reasoning strategy (ies) used for the topic by experts at the beginning of each section.*

There are a couple of instances of **mandatory** lectures (your module directors will inform you of these circumstances). All small group sessions are **mandatory** and you will rotate small group times throughout the pre-clerkship period.

In the **lecture** (**30 min**), the general **goals are:**

1) teach relevant terminology (**semantic competence**)  
2) review pertinent pathophysiology, and  
3) illustrate a practical approach to the topic.  
4) clarify common points of confusion regarding the reasoning approach to the topic

In the **small group sessions** (**most are 70 minutes**) the goals are:

1) Illustrate major diagnostic entities (common and/or serious) for the topic  
2) Teach typical “patterns” of presentation for these diagnostic entities and key decision points to assist with arriving at the diagnosis. This includes recognizing problems and constructing problem lists, building semantic competence (i.e. medical terminology), comparing and contrasting similar diagnoses seen with the topic, and formulating a differential diagnosis that the student can defend with the presenting data.
The aim is to move from the syndrome to disease. At times we will also introduce you to therapies for the topic at hand (Manager or “P”, i.e. plan, of the SOAP note). Your pharmacology course will also emphasize management principles in conjunction with this course. This course is not meant to serve as a comprehensive review of diagnoses that will be seen in the clerkships. ICR illustrates a variety of diagnostic reasoning techniques through examining a series of common symptoms, physical exam findings, laboratory test abnormalities and syndromes. The approach in ICR is consistent with current clinical reasoning theory.
Course Materials

In the ICR syllabus which will be distributed with each module, you will be provided with (1) summaries of each of the topics to be discussed, to include learning objectives for each session; (2) small group cases for each of the topics; (3) questions to serve as a guide in discussing the cases; (4) recommended readings; (5) selected references and (6) practice questions and answers.

Each small group will meet with a physician preceptor, at which time the cases for the topic will be discussed. **You should review the recommended readings prior to the session. Students will be expected to be familiar with the cases and the recommended reading materials, prepared to present a "problem list," discuss the differential diagnosis, appropriate clinical and laboratory findings/test as well as, integrate knowledge of basic science in the small group sessions.** In essence, students will be expected to participate (please review the below Small Group Grading Format for the course).

**Combined ICR/clinical skills sessions**

For these combined special sessions, you will be required to complete a one-page write-up (for the patient you examined) for ICR purposes. You will also be required to be prepared to give a 3-5 min summary of the patient that you saw during that clinical skills session. You will also have separate requirements for the clinical skills session.

A supplement to the syllabus (last page of the syllabus) provides a list of normal laboratory values for your convenience. Do not attempt to memorize this list—it is not core material for the course and will be provided with your ICR exams.

**Small group sessions** are designed to introduce clinical reasoning skills through the use of clinical scenarios and form the core of the Introduction to Clinical Reasoning Course. These sessions are felt by students and faculty alike to be valuable and productive educational experiences. These sessions are meant to model deliberate practice through applying your knowledge to common and/or life threatening presentations of the topic being discussed. *Preparation and active participation in the sessions are essential for successful completion of the course (see small group grading below).* You will receive your small group grades electronically (i.e. Google email). This email will include your small group grade and preceptor comments (as applicable) throughout the year.

**Small Group Grading Format:**

**B = “Bystander”:** This grade should be used for a student who is present at the small group session, but does not even demonstrate evidence of “observing” or watching the session and discussion (i.e., they are not paying attention). Other examples of “bystander” activities include studying other coursework or sleeping. Students demonstrating unprofessional behavior during the session, such as arriving late without a reasonable excuse or having distracting conversations during the session that do not pertain to the cases, should also receive this grade, since these behaviors may also lead to Department of Medicine Education Committee (DOMEC) review of overall performance. **Please annotate, on the front of the form, why the student is receiving**
this grade: i.e., arrived late, sleeping during session, studying other materials, distracting conversations.

**U** = **Unexcused absence** from the small group session.

**O** = “**Observer**”: This grade should be used for a student who is present at the small group session and is paying attention, but does not significantly contribute to the case discussions (i.e. they "observe" the session). An observer either makes no comments during the session, or their comments do not show evidence of preparation for the session. This could be due to a limitation in knowledge or in confidence. It may be manifest, for example, by a lack of basic understanding of the lecture notes or pertinent basic science concepts, and/or familiarity with the specific case scenarios. An observer does *not* show evidence of "participating" in learning the essential, basic information prior to or during the session.

**P** = “**Participant**”: This grade should be used for a student who “participates” in discussions, demonstrating reasonable preparation for the small groups through their questions, comments, and responses to the case study scenarios during the session. A “participant” demonstrates sound understanding of pertinent pathophysiologic and basic sciences principles and has the confidence to contribute this information in the group discussions. A "participant" can summarize the basic facts of the case and provide a basic problem list and a basic differential diagnosis when prompted.

**E** = “**Editor/Synthesizer**”: This grade should be used for a student who is able to “edit” the paper cases—they can recognize and summarize the key features of the case, selecting what data is important from what data is irrelevant for making the diagnosis. An editor can develop a prioritized problem list and a differential diagnosis of three or more reasonable options as well as select appropriate “next steps” and/or asks higher-level questions in the case evaluations. An editor also demonstrates the confidence to raise salient issues during the session that often directs, and may lead, further discussion. Editors demonstrate exceptional preparation and participation, and within the limits of the small group discussion format, appear like third year students who are progressing from “reporter” to “interpreter” (or beyond). This grade should be awarded to no more than 1/3 of the small group.

Students are expected to be prepared, informed, and enthusiastic during case study sessions (i.e. be **participants**). Being prepared and informed requires that the student study the appropriate syllabus materials, be familiar with information presented in the lecture as well as the recommended textbook readings, and review the case study scenarios. Additionally, students are expected to review basic science concepts pertinent to the case study. Enthusiasm refers to active participation in small group sessions. Students, judged by the preceptor to meet these criteria, will receive a grade of **Participant** for the case study session.

At the end of the year, the class mean and standard deviation in the small group sessions will be calculated. The number of standard deviations of your score from the class mean will be added (or subtracted) from your small group final point total, not to exceed 2 points.

**Bystander** and **Unexcused Absence** grades will be handled separately at the discretion of the Course Director.
Some “Tips” Regarding Success in this Course:
Expertise in medicine cannot be developed overnight and indeed studies of expertise from multiple fields cite the 10 Year Rule (10 or more years, equating to at least 10,000 hours, of deliberate practice being needed to develop expertise)! This is an introductory course meant to help you excel on the clerkships next year. Some tips for excelling in this course include:

1. **Know your objectives.** These objectives will be the emphasis on your examinations.

2. **Prepare for the small groups.** Review your readings and answer small group questions for cases in advance. This will help you get the most of each session. When you read your textbooks, pay attention to key clinical features, terminology, and comparing and contrasting related diagnoses.

3. **Practice, practice, practice!** This is critical with developing reasoning skill. In addition to the quizzes and small group cases, I have a number of practice question and answer books as well as additional CIPs (Clinical Integrative Puzzles) to help you prepare. The small group and quiz assignments (working in groups) is meant to facilitate your understanding and success.

4. **Appreciate the importance of self-regulation.** Self-regulation is defined as self-generated thoughts, feelings, and actions to achieve goals (Zimmerman, 1989). Self-regulation is often broken down into 3 phases: **forethought, performance, and self-reflection.** Components of the **forethought** phase include setting reasonable process and outcome goals--i.e. pacing with reading materials, effort with solving cases (process) and learning the objectives (goals). Also, be mindful of goal orientation which refers to the perceived value of the task—i.e., learn so that you can excel next year as opposed to just passing the test! **Performance** phase tips include positive self-instruction (believe in your capacity to excel!), task strategies (i.e. applying reasoning tools in the course, mnemonics, note taking, practice questions), time management (budget time for this course), help seeking (practice your skills with peers and superiors). **Self-reflection** tips include setting reasonable self-evaluation standards of performance (don’t set the bar too high or too low—if you want to talk more about this, see your course director), seeking causal attribution to errors to improve performance (self-directed learning which is perhaps the most important skill acquired during medical school), and attempt to optimize self-satisfaction (remember why you came to medical school!).

5. **Further develop your practical thinking skills.** A variety of investigators have studied improving practical thinking skills which should relate to clinical reasoning (Sternberg 1988, 1997; Gardner 1999). Five themes from this literature have emerged that may help you in this course: knowing why, knowing self, knowing differences, knowing process, and revisiting
   a. **Knowing why**—why is clinical reasoning important? Why is learning subject X important?
   b. **Knowing self**—recognize your personal strengths and weaknesses so that you can improve
   c. **Knowing differences**—learn to distinguish importance and use of clinical reasoning tools as well as comparing and contrasting related diagnoses
   d. **Knowing system**—understand the system we work in both in terms of strengths and limitations; understand that your resources may differ based on your practice environment
e. Revisiting—reflect on what went well and what needs to improve. Seek the assistance of peers and superiors to help you with this. Ask for references and/or additional readings to help further build your knowledge. Below is a “quick guide” given to students on the internal medicine clerkship which may help you.

6. What do you need to know (From USUHS internal medicine clerkship handbook)

Use this format to quickly self-assess in practical terms your knowledge of important, common issues for your own patients as well as other patients on your ward team or those discussed during preceptor rounds.

"WHAT DO YOU NEED TO KNOW?" – about a disease or syndrome

I. DEFINITION

- Can you explain to another what the label means? What it includes/excludes?
- Diagnosis: Complete diagnosis, classification (Is there a further classification or "staging"?) How is the diagnosis made? (When can we be sure the patient has the "label" that is proposed?)
- Pathophysiology (NON-NEGOTIABLE information, you must know this).

II. CLINICAL PICTURE

- Symptoms, Signs, Lab (How does each reflect pathophysiology?)
- Who is at risk for this disease? How common is it? Can it be prevented?
- How do age, gender, race, ethnicity, affect prevalence and presentation?
- Differential Diagnosis (What else can look like this?)
- Natural history (What happens, if you do nothing, in most patients?)
- Complications (What's the worst, in how many patients?)
- Effect on deployability.

III. TREATMENT (Also see "About a Specific Therapy" below)

- Options for treatment: Medical/Lifestyle/Surgical/Radiation (Does treatment alter the pathophysiology? Mechanisms)
- Treated history - Is there a standard therapy? How good is it compared to natural history? What should be followed?
- Safety (How "bad" is therapy, risk, costs and pitfalls?); alternate therapies

"WHAT DO YOU NEED TO KNOW?" - ABOUT A TEST (Again, there are three things)
• How does it **work**? (How does it address the physiology or anatomy? How will we use the result?)
• How **good** is it? (sensitivity, specificity, reproducibility; predictive value)
• How **bad** is it? (risk of the procedure, costs, financial and otherwise)
• What are the alternatives?

"WHAT DO YOU NEED TO KNOW?" - ABOUT A SPECIFIC THERAPY

1. How does it **work**? (affecting the anatomy or physiology; if a drug, pharmacology; what are the indications?)
2. How **good** is it? (efficacy - short term, long term - are there relapses? how good is the evidence?)
3. How **bad** is it? (risks, side effects, costs; contra-indications); alternatives?

Reading for this basic information about diseases, syndromes and tests will have immediate rewards.

We hope you enjoy the course!
Welcome to ICR! This course will introduce you to a variety of principles in clinical reasoning. You can consider clinical reasoning as a “toolbox” of methods that a physician uses to establish the diagnosis (and therapy) for a patient; this course will be focused primarily on diagnosis whereas pharmacology will introduce you to treatment. This course will help teach you how to transform a patient's history, physical examination and laboratory data into a problem list and differential diagnosis. We will also introduce you to tests that you can use to refine your diagnostic decisions. This is a course on "clinical pearls" or, in the words of Paul Cutler, "how to turn your patients' data into diagnoses".

The process of making a diagnosis is, at times, analogous to detective work. At its most fundamental level, it is an exercise in problem-solving. As in learning to perform a complete physical examination (clinical skills courses), learning how to generate a differential diagnosis involves working through a series of steps. Eventually, you will develop your own methods and shortcuts that emerge with increasing experience and expertise. Indeed, expert diagnosticians often perform these steps simultaneously. I will outline in the highlights in clinical reasoning section some of the tools that physicians use to work through these steps. We can summarize these steps accordingly:

1. Establish the database
2. Construct a problem list
3. Identify a key finding
   - or -
   Group a constellation of findings
4. Formulate a differential diagnosis
5. Synthesize a diagnostic hypothesis
6. Test the hypothesis

We'll expand on each of these steps as we work through the reasoning process.

1. Establish the database

As with any multi-step process, the first step is essential—success in subsequent steps hinges upon successful completion of the first step. At this stage, your task is to collect all the relevant facts of the case. This step is the province of the clinical skills course sequence--learning how to perform a thorough history and physical examination. This includes not only collecting the facts as presented by the patient but also knowing which review of systems (ROS) questions to ask to help you refine your diagnostic hypotheses. Indeed, formulating the differential diagnosis begins with collecting the history.

As at the “scene of the crime”, if you will, important clues may be everywhere to include hiding in plain view sometimes. The “case” may be solved by identification of a mole on the scalp, a
hemorrhage under the fingernail, or decreased pedal pulses. Likewise, the case may be solved through thoughtful consideration of the details that led up to the "crime". Identification of the family history of breast cancer or coronary artery disease, a remote travel history, or the almost-forgotten sexual encounter may be the most important clue to the diagnosis. Rarely, laboratory and x-ray findings may provide the essential details to solve the case. Typical basic laboratory studies upon admission to the hospital include chest x-ray, ECG, serum electrolytes, glucose, kidney function indices (BUN and creatinine), liver function tests (serum ALT, AST, alkaline phosphatase, and bilirubin), complete blood count with differential, and urinalysis.

At this stage, you want to make a complete list of all the potentially relevant facts about the case: the facts include presenting symptoms, other relevant medical history, physical findings, and pertinent laboratory and radiographic values.

In this course, we will provide the majority of the facts (database), in the form of "cases". This **DOES NOT** diminish the importance of learning how to perform a history and physical examination—these skills are essential for success in your clinical clerkships and future career! You will have the opportunity to further hone your history and physical exam skills in your clinical skills courses during the pre-clerkship time frame.

2. **Construct a problem list**

The problem list derived from your comprehensive database, but it is not the same! The problem list represents your efforts at interpreting what the facts mean, and how they fit together. It is therefore a **synthesized** product. Upon reviewing your patient's history, physical and laboratory data (the database or facts) you extract, prioritize and interpret the various abnormal symptoms such as "abdominal pain" or "visual loss"; physical examination findings like "nail lesion", "heart murmur", "leg swelling"; and abnormal studies such as "anemia", "renal failure", "chest x ray opacity". Be as specific as possible with constructing your problem list to help you refine (i.e. "shorten" the list) the diagnostic possibilities. To illustrate: "acute right upper quadrant abdominal pain" is preferable to "abdominal pain", "episodic monocular visual loss of the left eye" rather than "visual loss"; "splinter hemorrhage" as opposed to "nail lesion", "acute unilateral edema" versus "leg swelling", "acute microcytic hypochromic anemia" is better than "anemia" as the list of potential diagnoses is much shorter with the former as opposed to the latter!

There are two basic approaches to constructing the problem list, each of which has its own merits and drawbacks. However, it is necessary to learn how to apply either strategy, as actual clinical practice involves using both strategies (sometimes both strategies are used in the same patient). The two basic approaches are "splitting" and "lumping". With "splitting", one "splits", or lists, each symptom, relevant other historical detail (i.e. family history of breast cancer), physical finding (i.e. S3), and lab abnormality (i.e. acute hypercalcemia) as a separate problem. Hence, the problem list closely resembles the comprehensive list of facts. In "lumping", the clinician attempts to group, or "lump", symptoms, exam findings, and lab abnormalities from the comprehensive list of facts into a single problem (Occam's razor).

Let's look at an example to illustrate these two problem-solving approaches:
A 40 year-old male soldier reports to sick call with a complaint of fever to 103 degrees F accompanied by shaking chills, intermittently during the past two weeks, since returning from Iraq. He reports having had rheumatic fever as a child, and has been told of an "innocent" heart murmur since childhood. On physical exam, his nail beds reveal splinter hemorrhages and he has tender subcutaneous nodules along several digital margins. Cardiac auscultation reveals a Grade II/VI diastolic rumble and an opening snap over the apex. His chest X ray is unremarkable. Serum chemistry studies are normal. CBC reveals an elevated white blood count of 18,000 with PMN predominance and 10% band forms. His hemoglobin/hematocrit are 11 gm/33%, respectively.

Problem List, Step 1: Establish the database (list all the facts)

1. High fever (103 degrees)
2. Rigors (shaking chills)
3. History of rheumatic fever
4. History of heart murmur
5. Splinter hemorrhages
6. Tender subcutaneous nodules (Osler nodes)
7. Apical diastolic "rumbling" heart murmur
8. Leukocytosis (neutrophil predominance with "bandemia")
9. Anemia with normal MCV (normocytic normochromic anemia)

Problem List, Step 2: Construct the problem list (edit the database)

Try both "lumping" and "splitting" as you approach differential diagnosis during this course. Expert diagnosticians use the approach that is most advantageous to the case at hand.

"Splitter" Problem List
1. Fever
2. Splinter hemorrhages
3. Osler nodes
4. Diastolic heart murmur, consistent with (c/w) mitral stenosis
5. Leukocytosis with bandemia
6. Normocytic normochromic anemia

Characteristics of the "Splitting" Approach:
1. Completeness--every abnormality and every symptom is addressed
2. Establishes maximum opportunity to identify the key finding and correct diagnosis through thoughtful consideration of the differential diagnosis of each problem (diagnoses which show up repeatedly may be most likely)

Potential weaknesses of the "Splitting" strategy:
1. Does not emphasize the clinician's creativity to link symptoms and findings together
2. Can lose "forest" (how to group problems together) for "trees" (individual problems)

**Cases well-suited to "Splitting":**
1. Unfamiliar or rare scenario
2. No diagnostic hypothesis after gathering the facts (i.e. you're clueless--it happens to everyone!)
3. Complicated patient presentation with multiple diagnoses (i.e. intensive care unit patient)

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"Lumper" Problem List

1. Probable Endocarditis
   1a. Fever/embolic skin lesions/leukocytosis/normocytic anemia
   (The clinician makes the leap of faith that these individual findings are due to the same cause)
   2. Probable mitral stenosis

**Characteristics of the "Lumping" Approach:**
1. Emphasizes pathophysiologic grouping of individual problems
2. Emphasizes creative problem solving

**Potential weaknesses of the "Lumping" strategy:**
1. Premature closure (you miss the diagnosis by “oversimplifying” the case)
2. May omit a key detail

**Cases well-suited to "Lumping":**
1. Familiar or classic presentation of a disease
2. Unifying diagnostic hypothesis generated with database

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3(a). **Identify a key finding**

When using a "splitting" strategy for your problem list, this is often the next step. Here, you want to identify the most unique and/or most serious items on the problem list and explore the differential diagnosis of each. It also can be very helpful when you identify problems with a clearly defined and limited set of diagnostic possibilities--examples would include "anion gap metabolic acidosis", "hypercalcemia", or "hypochromic microcytic anemia".

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3(b). **Group a constellation of findings**

If you're a "lumper", you've already started this process. If you're a "splitter", it's wise to manipulate the comprehensive problem list in every way that makes pathophysiologic sense to attempt to identify syndromes and/or shorten the potential list of diagnostic possibilities. To use our example of the 40 year old soldier with fever, it would be helpful to combine fever with at
least one other problem to consider diagnostic possibilities, since the causes of fever alone are so numerous. Groupings which would be appropriate to this case would include "fever and rash (skin lesions)", or "fever and heart murmur". "Fever and leukocytosis" and "fever and anemia" will generate very long lists of possible causes. Re-group the problems differently if your diagnostic hypotheses prove to be incorrect.

4. **Formulate a differential diagnosis:**

A differential diagnosis is nothing more than a list of realistically plausible explanations for a patient’s presentation. When you look the differential diagnosis for a given problem in a textbook, the list is often exhaustively long. Only consider diagnoses that are realistic and plausible based on the patient’s database—careful attention to the patient’s context will eliminate “shot gun” medicine. For example, consider age, ethnicity, other symptoms, co-existing medical conditions, and prior work-ups to establish what entities are realistically plausible. To return to our prior example, sickle cell disease might account for the patient’s anemia if he is of African-American ancestry, but it is not realistic if he is Caucasian. Even if he is African-American, it is not plausible to consider sickle cell if we can verify multiple past negative screening studies for the disease.

A good rule of thumb is to try to come up with **at least three to five possible explanations** for the patient's problem. You may need to consider more, depending on your confidence in the diagnosis possibilities and the thoroughness of your database.

There is no single approach to formulating a differential diagnosis. Some examples of strategies (which are often used in combination) include:

1) **Organ System Approach:** This approach may be well suited for a problem such as "chest pain". You might consider cardiac causes (i.e. ischemia, pericarditis), pulmonary causes (i.e. pneumothorax, pulmonary embolism), gastrointestinal disease (i.e. gastroesophageal reflux or peptic ulcer), musculoskeletal disease (i.e. costochondritis), and vascular disease (i.e. aortic dissection).

2) **Anatomic Approach:** This approach can be helpful for problems such as "dysphagia", where we might consider upper cricopharyngeal neuromuscular disease (myopathy, cranial neuropathy, motor neuron disease), esophageal webs and strictures, esophageal tumors, and disorders of lower esophageal motility (achalasia, diffuse esophageal spasm).

3) **Pathophysiologic Approach:** Such an approach may be well suited to a problem such as "thrombocytopenia", where one may consider explanations involving decreased platelet production (chemotherapy/drug-related myelosuppression; marrow infiltration by fibrosis and/or tumor); increased platelet destruction (consumptive coagulopathy--DIC, TTP, etc.; autoimmune thrombocytopenia); and increased platelet sequestration (hypersplenism).
4) Mnemonic Approach: There are a variety of examples that can be used! See also highlights from clinical reasoning theory for explanation of tools and additional approaches for formulating differential diagnoses.

5. Synthesize a diagnostic hypothesis

This step represents "the moment of truth" in the clinical reasoning process. After gathering the database, creating a problem list, and formulating a differential, you commit to a diagnosis. Knowingly or not, you think, because of what I know about this patient (i.e. age, sex, symptoms and co-morbid diseases) I believe that "X" is the most likely diagnosis. This sort of reasoning is inclusive. At times, however, despite your confidence in your diagnosis, you recognize that the patient could plausibly have a different, potentially serious, diagnosis. In this circumstance, consciously or not, you think "because of the following facts (i.e. age, associated symptoms, or risk factors for a disease) the patient could have diagnosis X, Y, or Z. I want to “rule them out”. This so-called "rule-out" strategy is often employed when serious diagnostic possibilities are plausible given the patient's presentation. It is exclusionary in nature. This strategy is commonly used in the approach to the diagnosis of chest pain in middle-aged adults. In such cases, diagnoses such as pulmonary embolism, myocardial infarction, tension pneumothorax, pericarditis, and dissecting aortic aneurysm are specifically "ruled out" by appropriate testing. We will consider the approach to "Rule-In" and "Rule-Out" strategies in the next section.

I think that it can be very helpful to write down the history, physical exam, and laboratory data "for" and "against" your diagnostic possibilities to help you "weigh" the data and commit to a diagnosis. When you read about diseases, try to compare and contrast contextual features (i.e. demographics, risk factors, and typical associated findings), physical findings, as well as laboratory and radiographic tests between diseases that can present in a similar fashion—this will help you to recognize the diagnoses when you see it in practice.

6. Test the diagnostic hypothesis

Testing a diagnostic hypothesis generally involves syndrome and/or disease specific studies (i.e. laboratory tests, x-rays, biopsy). Which tests to select depends on many factors, to include your level of confidence in your diagnosis as well as whether your primary strategy is inclusive ("ruling in") or exclusive ("ruling out"). We have already highlighted that serious conditions to be "ruled out" should be realistic and plausible for the patient at hand (i.e. you would not consider a diagnosis of prostate cancer in a woman!).

If a diagnosis is both realistic and plausible, an additional factor to consider is the prevalence of the disease in a population with your patient's demographic characteristics. In the example of our 40 year old with fever, skin lesions, and a mitral stenosis heart murmur, the likelihood of endocarditis is high (probably 70% or greater likelihood). This fact-based estimate is called the
**pre-test probability of disease.** Testing diagnostic hypotheses should take this estimate into account.

Expert clinicians recognize that diagnostic hypothesis testing is, in large part, considering and acting on probabilities. We try to maximize the probability that our diagnostic hypotheses are correct, and minimize the probability that these hypotheses are incorrect. The appropriate study for testing your diagnostic hypotheses can differ based on your pre-test estimate of the probability of disease.

<table>
<thead>
<tr>
<th>Pre-test Probability</th>
<th>Diagnostic Strategy</th>
<th>Test Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&quot;Rule Out&quot;</td>
<td>High Sensitivity</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&quot;Rule In&quot; &amp; &quot;Rule Out&quot;</td>
<td>High Sensitivity &amp; High Specificity</td>
</tr>
<tr>
<td>Low</td>
<td>&quot;Rule In&quot;</td>
<td>High Specificity</td>
</tr>
</tbody>
</table>

An acronym from the Schwartz Physical Diagnosis Text is helpful in recalling these principles--Remember "SpPin" and "SnNout". These abbreviations stand for “Specific tests when Positive help to rule in disease” and "Sensitivite tests when Negative help to rule out disease”.

Let’s review a 2 x 2 table to illustrate some basic statistical principles. Disease Present vs. Disease Absent is on one axis, and Test Positive vs. Test Negative is on the other.

<table>
<thead>
<tr>
<th></th>
<th>Disease Present (D+)</th>
<th>Disease Absent (D-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Positive (T+)</td>
<td>&quot;True Positives&quot; (TP)</td>
<td>&quot;False Positives&quot; (FP)</td>
</tr>
<tr>
<td>Test Negative (T-)</td>
<td>&quot;False Negatives&quot; (FN)</td>
<td>&quot;True Negatives&quot; (TN)</td>
</tr>
</tbody>
</table>

In an ideal world, all patients with a positive test would have the disease, and all patients with a negative test would not have the disease (or 100% positive and negative predictive values respectively). In reality, even our “best” tests aren’t this good. Those which come closest are considered "gold standards". Examples of “gold standards” include coronary angiography for coronary artery disease, lumbar puncture for meningitis, and serum HCG for the diagnosis of pregnancy. In urgent situations, whereby delay in diagnosis and therapy could lead to an adverse outcome, it may be warranted to move quickly to “gold standard” diagnostic testing (which is often more invasive and expensive than “less ideal” tests). In less urgent settings, use of "less ideal" tests is often appropriate, due to patient acceptance and

---

**Performance Characteristics of Tests**

**Sensitivity** = Proportion of patients with the disease who have a positive test. Mathematically, it is expressed as True Positives/(True Positives + False Negatives). Or, true positives/all patients with disease.
Specificity = Proportion of patients in whom the disease is absent who have a negative test. Mathematically, it is expressed as True Negatives/(True Negatives + False Positives). Or, true negatives/all patients without disease. The "false positive rate" can be calculated from the specificity:

\[
\text{False positive rate} = 1 - \text{specificity}
\]

Sensitivity and specificity are not affected by disease prevalence.

Positive Predictive Value = The proportion of patients with a positive test who have the disease. Mathematically, it is expressed as True Positives/(True Positives + False Positives). Or, true positives/all positive tests

Negative Predictive Value = The proportion of patients with a negative test who don’t have the disease. Mathematically, it is expressed as True Negatives/(True Negatives + False Negatives). Or, true negatives/all negative tests.

The positive and negative predictive values are affected by disease prevalence.

Over and over, you will encounter descriptions of the sensitivity and specificity of various clinical tests in the medical literature. Keep in mind, however, that actual test performance in clinical practice is highly dependent on the prevalence of the disease (clinical practice questions involve predictive values, i.e. the “denominator” is all individuals with positive or negative test results).

Let's use our 40 year-old patient again as an example. Let’s assume that a patient with his symptoms and physical findings has a pre-test probability of disease of 80%, or .8, for endocarditis. To make the math simple, this would estimate that out of 1000 patients with a similar clinical picture, 800 would have endocarditis, and 200 would not. In this case, we'd like to do blood cultures as a diagnostic study (this is virtually the gold standard for this diagnosis, provided that the patient hasn’t received antibiotics in the recent past). We'll assume that the sensitivity and specificity of this test are both 0.99.

Next, set up a 2 x 2 table:

<table>
<thead>
<tr>
<th></th>
<th>Endocarditis +</th>
<th>Endocarditis -</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Cultures +</strong></td>
<td>TP = 800 x 0.99 = 792</td>
<td>FP = 200 x 0.01 = 2</td>
</tr>
<tr>
<td><strong>Blood Cultures -</strong></td>
<td>FN = 800 x 0.01 = 8</td>
<td>TN = 200 x 0.99 = 198</td>
</tr>
<tr>
<td>n = 800</td>
<td>n = 200</td>
<td></td>
</tr>
</tbody>
</table>

In this example, the positive predictive value of blood cultures will be TP/TP + FP, or 792/(792 + 2), or 0.999. Likewise, the negative predictive value of blood cultures will be TN/TN + FN, or 198/(198 + 8), or 0.961. Notice that the negative predictive value, in this case, is not as "good" as the positive predictive value. This finding emphasizes the influence of the pre-test probability of disease on actual test performance!
There is one additional and clinically useful concept to be derived from our example—the **post-test probability of disease**. Although we often don't calculate the post-test probability mathematically in actual practice (and therefore you won't be asked to calculate post-test probabilities on examinations), the purpose of performing a study to test your diagnostic hypothesis is to effect (and hopefully advantageously “refine”) the post-test likelihood of having a disease. **Post-test probability** can also be estimated from the **positive and negative predictive values**.

Returning to our above example, assuming you are curious about how to perform this calculation, first you need to determine the likelihood ratio (LR) for a positive blood culture (or the likelihood ratio for a positive test). The likelihood ratio, for a positive test, will be \((TP/TP + FN)/(FP/FP+TN)\). Based on our definitions of test performance characteristics above, this formula simplifies as follows:

\[
LR^{\text{Positive}} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}
\]

In our example from above, the numbers work out as follows: \((792/800)/(2/200) = LR^{\text{Positive}} = 99\).

Next, you need to convert the pre-test probability to pre-test odds. Pre-test odds is simply the ratio of the pre-test probability of having the disease divided by the pre-test probability of not having the disease. In our current example, the pre-test odds of endocarditis would thus be: \(0.8/(1 - 0.8) = 0.8/0.2 = 4\).

The next step is calculating the post-test odds from the following equation:

\[
\text{Pre-test odds ratio } \times LR^+ = \text{the post-test odds}.
\]

In this example, it will be \(4 \times 99 = 396\).

To convert post-test odds back to a probability, you can use this formula:

\[
\text{Probability} = \frac{\text{Odds}}{\text{Odds} + 1}
\]

In our example, then, you would divide 396 by 397 to establish the post-test probability of disease well beyond 0.99. In this example, endocarditis would be very likely if blood cultures were positive!

What if the blood cultures were negative? What would be the post-test probability that this patient has endocarditis? In this instance, we would need to calculate the likelihood ratio for a negative test (\(LR^{\text{Negative}}\)), which would basically be \((FN/TP + FN)/(TN/TN + FP)\). This formula simplifies as follows:

\[
LR^{\text{Negative}} = \frac{(1 - \text{Sensitivity})}{\text{Specificity}}
\]

Using our example, \((8/800)/(198/200)=LR^- =0.01\).

To calculate post-test probability, again you would first convert pre-test probability to pre-test odds or as illustrated above .8/.2 = 4.

Next, multiply pre-test probability \(x LR^{\text{Negative}}\). Hence, \(4 \times 0.01 = 0.04\).
Finally, convert post-test odds to post-test probability. In our example, \( \frac{0.04}{0.04 + 1} \), or 0.038.
Therefore, with negative blood cultures, there is only a 3.8% chance that our patient would have endocarditis! With that finding, we should carefully consider alternative diagnoses!

**Summary of Diagnostic Test Principles**

1. Sensitivity and specificity are not influenced by disease prevalence.
2. Predictive values are influenced by disease prevalence.
3. The questions asked in clinical practice involve predictive values. (i.e. does *this* patient with chest pain have coronary artery disease?)
4. Sensitive tests, when negative, help to rule out a disease. “SnNout”
5. Specific tests, when positive, help to rule in a “SpPin”
6. Tests are most influential for diagnostic hypothesis testing at intermediate probabilities of disease. (Just for fun, try changing the numbers in our example from 800 : 200 to 500 : 500, keeping sensitivity and specificity the same!)

**Selected Highlights from Clinical Reasoning Theory**

*“Tools of the Trade”*

Clinical reasoning involves the use of a variety of strategies or tools to help the physician efficiently, effectively, and accurately establish the diagnosis and therapy. In other words, clinical reasoning tools allow for competent care of patients which I like to refer to as bringing everything to the encounter that is needed and nothing more. Some tools used in clinical practice by expert physicians include the following. Please keep in mind that a variety of strategies may be used in a given encounter (they are not mutually exclusive). *We will illustrate the use of these tools or strategies throughout the ICR course. Indeed, several sections of your syllabus will identify the reasoning strategy(ies) being illustrated.* These tools or strategies are not listed in order of preference.

1. **Probabilistic/Bayesian**—This has been illustrated in this note set/above example of a patient with possible endocarditis. It involves explicitly applying statistical principles (i.e. sensitivity, specificity, predictive values) to the specific clinical encounter/diagnostic or therapeutic question being asked. This requires a relatively high amount of cognitive effort. We will also introduce you to *evidence based medicine*, a form of Bayesian approach, in this course and we will have a lecture/discussion on this topic.

2. **Heuristics**—These are cognitive shortcuts. For example, consider meningitis in all patients who present with fever and mental status changes. Consider myocardial infarction in all patients who present with chest pain and ECG changes. The relatively low cognitive effort with use of these “rules of thumb” can help you; know the limitations (or exceptions to the rule, if any) with using these “shortcuts”.

3. **Hypothetico-deductive reasoning**—This strategy involves considering a diagnosis (hypothesis) in isolation, based on all the presenting data (deductive). For example, in a patient presenting with chest pain you may consider myocardial infarction. MI is then the
hypothesis and one looks at the data to deduce (deduction) if this is the diagnosis. If not, another diagnosis, such as gastroesophageal reflux disease (GERD) would be considered. The clinician would go back to the beginning see if the patient’s symptoms and their observations fit GERD. If GERD doesn’t fit, another option such as pulmonary embolism (PE) could be considered. The clinician would go back to the beginning see if the patient’s symptoms and their observations fit PE. This reasoning strategy requires high effort and is frequently used by novice clinicians.

4. **Schemas**—Schemas can be thought of as flow charts or algorithms. Schemas are based on the notion that something cannot be true and not true simultaneously. In a schema, the clinician is asked to go through a series of prioritized steps where at each step the presence or absence of practically any symptom, observation, laboratory or radiograph is determined. Based on the presence or absence of the finding, a subsequent step is solved (with a shorter list of potential diagnostic entities). Schemas are commonly used by novice clinicians and are occasionally used by experts. A modification of schemas involves *concept maps.* A concept map is a schematic device for representing a set of concept meanings in a framework of propositions (Novak and Govin, 1984). To create a map, begin with defining a problem or issue that the map will address. Next, identify and list key concepts that apply to the map (more specific concepts that relate in some way to the general concept). As you build the map (see examples below), tie concepts together with *linking words* (examples: causes, manifested by, resulting in, is treated by, such as, can be, is defined by). Studies have demonstrated that these maps can help learners both organize ideas as well as facilitating understanding (both a teaching and learning method). You can access a free, not for profit, concept map tool (Cmap tool) for constructing your maps from http;cmap.ihmc.us

5. **Key finding (key feature)**—In this reasoning strategy, the clinician focuses on a problem from the problem list (also known as a finding or feature) with a very limited differential diagnosis. For example, a patient may present with joint pain, fever and an erythrocyte sedimentation rate (ESR) of 120. Focusing on the ESR to generate an initial differential diagnosis would be a reasonable approach in this case as a very small number of diagnostic entities can present with an ESR over 100.

6. **Pattern recognition**—This tool is the proverbial diagnosis at a glance that is often used by expert clinicians. Given the patient’s presenting symptoms and findings the diagnosis immediately comes to mind (the pattern is put together). This requires little cognitive effort and is based on years of experience and deliberate practice. As an example, you undoubtedly recognize the many forms of a chair and don’t have to think about the component parts to make this determination. Likewise, you recognize the component parts of a door and opening a door requires little to no cognitive effort whereby for a young child, where this “pattern” has not been established yet, this can be quite a challenge. The literature supports the notion that with growing expertise, we use this form of reasoning more and more frequently as it allows one to efficiently and accurately arrive at the diagnosis in many cases. This is not to say that you shouldn’t use this approach as a novice clinician as indeed using pattern recognition with deliberate confirmation with one of the above strategies has been shown to lead to improved diagnostic accuracy over sole use of one or more of the above
approaches alone (see clinical reasoning references on Sakai site). You should, however, use this (as well as other “short-cuts” with caution at your stage of training.

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**jaundice**

is defined as

yellow pigmentation of the skin due to

excess bilirubin can be caused by

impaired conjugation impaired uptake increased production

liver disease can include

hepatomegaly is characterized by

right upper quadrant pain

may be suspected if

h/o of viral hepatitis such as hepatitis C

h/o of medication that induce liver toxicity
Emerging Understanding of Expertise

The reasoning literature suggests that the following processes occur as we develop clinical reasoning expertise. Please see references for more details (if you are interested, many are on the course Sakai site). Also, if you’d like to chat about opportunities for research projects in this field (if you are really interested in this subject), feel free to set up a time with me. Please also see tips for success in intro policies and procedures section of the syllabus. This course will emphasize topic specific content and reasoning techniques (tools) for establishing the diagnosis.

1. **At first, learning how to establish a diagnosis from presenting patient information is very effortful.** You will likely find this to be difficult and time consuming. Typically learners use the hypothetico-deductive approach. This approach is not to be discouraged as it can help you with building *illness scripts* (prototypes of what is expected in a diagnosis; all the symptoms and observations that can be seen thus leading to “chunking” of presenting information or pattern recognition skill). Practice is essential and the literature would suggest the more deliberate practice, the better. Spend time preparing for small group discussions and talk to your colleagues with answering quiz questions. Consider using practice question (and answer) books as further assist with applying your knowledge or deliberate practice efforts—I have some of these in my office which you can sign out. Probe the knowledge and experience of your
clinician expert teachers in your small group sessions. You may even want to consider a shadowing experience through one of USU’s interest groups.

2. **Identifying the intermediate steps to establishing the diagnosis likely fosters the development of expertise.** This is one of the reasons for stressing *semantic competence* (proper terminology), problem list formation, comparing and contrasting related diagnoses, and learning how to defend your diagnostic decisions with presenting patient data is stressed in this course. This will foster the development of illness scripts for diagnoses to help you become more effective (and likely efficient) next year on the clerkships. Consider checking out CIPs (clinical integrative puzzles) which are clinical “crossword puzzles”, if you will, that emphasize intermediate key steps in helping you establish a diagnosis. Also consider constructing concept maps. You have examples of the latter in your Kocher’s textbook as well.

3. **The basic sciences are important for promoting diagnostic and therapeutic accuracy and effectiveness.** This refers to the concept of *encapsulation* or how experts compartmentalize or simplify presenting information to establish a diagnosis both in cases of certainty as well as uncertainty. Knowing anatomy, physiology, pathophysiology, microbiology, pharmacology, biochemistry and other basic science courses need to be stressed and we encourage you to review your notes from last year to help you in this course. We have also included brief, salient “basic science highlights” for several sections in this course and this syllabus is also cross-referenced with pathology (and vice versa). Also, to foster encapsulation, several of your course topics are discussions of syndromes (the step prior to the diagnosis, i.e. acute kidney failure) or laboratory data synthesis (metabolic acidosis or anemia).

4. **Experts sometimes have difficulty explaining how they specifically arrive at the diagnosis.** Can you describe the components of a chair or door to me? How about how a loved one walks or talks? Patterns can become so engrained or automatic that it’s tough to explain. What I would like to stress here is that you ask your teachers to provide needed explanations and if you are not satisfied, further consult your reading materials, the literature or your course director.

5. **Expertise is domain specific.** Establishing and maintaining expertise requires effort through deliberate practice. You need to learn specific techniques (or tools) in addition to content. We will emphasize both in this course. It therefore probably isn’t surprising that expertise is domain specific or limited. For example, I am not a good resource for automobile repair questions or pediatric issues as a general internist. This is one of the reasons that reading and referencing the literature throughout your training and future practice is critical to maintain your skills (self-directed learning). We hope to promote the development of this skill in this course (i.e. don’t challenge a quiz or exam question without giving me one or more references to support your claim).

6. **Context of the presentation matters.** We are in the process of incorporating strategies to increase the authenticity of the small group sessions (making the cases closer to what you will see next year in clinics and on the wards). Most of the sections in the course now begin with an introductory patient (or more) that is returned to at the end of the section. Also, what is the influence of demographic information such as age, gender and/or race in a given case? Please
also consider what you bring to the context—things you learned in HCHC are important (know your shortcomings, know-self) and please review self-regulation in preceding pages on optimizing success.

7. **Experts have more elaborate problem representations of their patients.** This is one of the reasons that we will stress problem list formation in this course and encourage you to compare and contrast similar diagnoses—i.e. what is the evidence for and against diagnosis X in this case? Along these lines, experts are able to “sift” the data, they know which facts are important and which facts are unimportant. This is something that we will introduce you to in this course. Practice this in your small groups with your preceptors—why is this fact important (or not important) in this given patient? Also, we will introduce you to the concept of degree of abnormality which is also critical in making diagnostic and therapeutic decisions. One’s differential diagnosis is much different for a patient with a temperature of 106°F vs. 101°F.

8. **Simple experience is not sufficient for the development (or maintenance) of expertise.** A long period of immersion of activities involving effortful practice of skill often under the direction of a coach or mentor is needed to develop and maintain expertise (deliberate practice). You need to put in time digesting and applying information learned in this course to develop expertise in clinical reasoning which is essential for your future success as a physician. Literature in multiple domains have also supported the 10 year rule (10 years or at least 10,000 hours of deliberate practice) to develop expertise in a complex skill. Don’t expect to become an expert this year and practice/hone your skills with your preceptors!

9. **Expertise is an adaptation.** Due to limits in attention and working memory, as you acquire expertise in clinical reasoning, problem solving becomes more automatic, freeing up cognitive “space” for processing information and responding in an efficient and effective manner. In other words, the literature suggests that in an expert’s domain (a cardiologist seeing a patient with a cardiac problem), clinical reasoning is largely pattern recognition due to the development of robust prototypes of illnesses in memory (known as illness scripts)—i.e. schemas, probabilities, key findings, essentials of basic science, and heuristics are idiosyncratically connected and used to solve patient problems. The expert can then use cognitive “space” for attending to nuances in the presentation and other contextual features that may be germane. As an example, for those of you who drive, adaptation in your skills over time (increasing automaticity, you don’t have to think about how to use the clutch, turn signal, etc.), allows you to focus attention on traffic and potential hazards, talking to friends or listening to the radio. This example of adaptation (expertise), allows you to more efficiently and effectively get to your destination. This is not to say that an expert always functions in the “pattern recognition” or “low cognitive effort or automatic mode”; indeed, one of the hallmarks of expertise is being able to recognize and interpret when things don’t fit a pattern and transition to one or more of the more effortful strategies (i.e. probabilistic, schema, hypothetico-deductive) to diagnose and/or treat a patient.
INTRODUCTION TO CLINICAL REASONING
LOW BACK PAIN (LBP)

Jess D. Edison, MD
Raul Marin, MD

A 48 year old Air Force Colonel presents with a two day history of pain in his back. He reports that the pain began shortly after lifting boxes while moving into his new office. The pain radiates down his left leg.

Questions:
1. What are his risk factors for low back pain?
2. What additional history and physical exam questions would help you establish the diagnosis in this patient?
3. What ancillary studies can you obtain in the evaluation of low back pain and when should these be performed?
4. What treatment options should be considered for this patient?

Objectives: At the end of this session, students will:
1. Describe the pathophysiology of Low Back Pain (LBP)
2. List the cardinal features of LBP in adult and children patients
3. List red flag signs and symptoms
4. Be able to generate a differential diagnosis of LBP in adult and pediatric patients
5. Describe the work up for LBP in adult and pediatric patients
6. List treatment options for LBP in adult and pediatric patients

Overview: Low back pain is a common problem in adults. This section of the syllabus will use basic illness scripts, schemas (algorithms), and heuristics in the approach to this diagnosis.

Epidemiology:
There is a 60-90% lifetime incidence and a 5% annual incidence of LBP in the adult population. LBP is mostly a self-limited disease process in most people where it does not advance to disability. Once LBP occurs, it is likely that it will recur in most subjects. Only a small percent (approximately 2%) of the LBP sufferers go on to develop disabling symptoms.

Among the general population, LBP is the leading cause of disability in people younger than 45 years of age. In adults above 45 years of age, it is the 3rd cause of disability. Among chronic LBP patients, the longer the subject is off work due to the back pain, the lower the chance that the subject will return to work (25% at one year; 0% at 2 years).

LBP is a common complaint during childhood and rare in those under 10 years of age. The incidence increases between 12-15 years of age and at the age of 11.5, 36% are expected to suffer from LBP. Most cases are acute episodes with limited health
In contrast, some children experience recurrent low-back pain that can lead to disabling consequences. Estimates of lifetime prevalence for low-back pain in children vary from 13-51%, point prevalence ranges from 1-33% and prevalence of recurrent low-back pain ranges from 7 to 27%. The prevalence of pain which necessitates medical consultation varies from 8-16%, and pain interfering with school and leisure activities varies between 7 and 27%.

**Common Pain Terms:**

- **Allodynia:** pain due to a stimulus *that does not normally* provoke pain
- **Analgesia:** absence of pain in response to stimulation *that would normally* be painful
- **Dysesthesia:** unpleasant abnormal sensation, whether spontaneous or evoked
- **Hyperalgesia:** increased response to a stimulus *that is normally* painful
- **Hyperesthesia:** increased sensitivity to stimulation, *excluding* the special senses
- **Hyperpathia:** painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold
- **Neuralgia:** pain in the distribution of a nerve or nerves
- **Neuropathic pain:** pain initiated or caused by a primary lesion or dysfunction in the nervous system
- **Nociceptor:** receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged
- **Protopathic pain:** burning, diffuse, and localized
- **Radiculopathy:** disturbance of function or pathologic change in one or more nerve roots
- **Radiculitis:** inflammation of one or more nerve roots

**Anatomy:**

1. Three-joint complex:
   a. Vertebral bodies & disc
   b. Facets
2. Pain generators: numerous structures have sensory innervation:
   a. Facets: sensory branches from 3 different segmental levels via the medial branches of the dorsal primary rami.
   b. Disc: sensory fibers to the outer 1/3 of the annulus fibrosus. The sinuvertebral nerve supplies the posterior aspect as well as the posterior longitudinal ligament.
   c. Paraspinal muscles: innervation from segmental levels.
3. Movement: additive effect of all levels. 80-90% of flexion and extension occurs at L5-S1 and L4-L5 (up to 20% movement per segment) because of the 90-degree orientation of the facets in the sagittal plane. This orientation allows only 2-3 degree axial rotation. Lateral flexion of each vertebra upon the next includes axial rotation, and vice versa.
4. Abdominal musculature: abdominal muscles act via thoracolumbar fascia in counteracting shear forces (create extension moment on lumbar spine as the subject flexes forward. Abdominal contraction also holds abdominal contents in while diaphragm pushes them down during straining, thus increasing intra-abdominal pressure and creating a rigid cylinder in support of the spine.
Pathophysiology:

1. Cascade of degeneration: the disc is the weak link. Slow degeneration and shrinkage of the disc leads to decreased tension of the anterior and posterior longitudinal ligaments (ALL & PLL) thus producing segmental dysfunction and instability. Weight is also shifted from the anterior elements (disc/vertebral bodies) to the posterior elements (facets). The anterior instability leads to calcification (spur formation) of the ALL & PLL. Increased weight shift to the posterior elements leads to osteoarthritic changes of the facets with associated spur formation and stenotic changes. All this extra calcium deposition leads to ankylosis and thus, stabilization of the segmental instability.

2. Biochemical issues: mechanical compression of the nerve is not necessary for the production of neuropathology. Evidence points to the aqueous contents (Phospholipase Alpha-2 being the most well-known) of the disc as being noxious to the nerve. Inflammatory changes occur within 5 days of exposure of the nerve to nucleus pulposus contents. Furthermore, there is no relationship between the size of disc herniation and symptomatology, such as asymptomatic subjects having evidence of herniation and root compression.

1. What are his risk factors for low back pain?

Risk factors:

Adults

1. Risk for acute LBP (< 6 weeks): occupational/work factors that expose workers to repetitive and forceful activities increase the risk of first episode/acute LBP (truckers, nurses, etc.). Other factors that increase risk are repetitive vibration exposure, trauma, and smoking.

2. Risk for chronic LBP (>6 weeks): time off work, poor job satisfaction, patient’s perception of “stress”, litigation/compensation (raising concern for malingering), psychological issues (depression, anxiety, somatization) history of previous LBP/back injury, history of substance/medication abuse, back (extensor) muscle weakness/decreased endurance, and poor cardiovascular fitness.

Children

The literature points out important risk factors for LBP: minimal physical activity, intensive sports, genetics, psychosocial factors, smoking, and leisure activities that have a high physical impact.

2. What additional history and physical exam questions would help you establish the diagnosis in this patient?

Diagnosis:

1. History and physical examination: this is the foundation of ALL diagnoses. Certain H & P issues can help the clinician in reaching a diagnosis. The below schemas (DoD
VA guidelines on LBP) represent a useful approach to the evaluation of the adult patient with low back pain.

2. It is important to stress the significance of red flags that warrant further diagnostic work-up. Knowing these red flags which warrant additional evaluation and/or treatment are essential for you to remember. For those patients without any red flags or medical conditions that may mimic acute LBP, a conservative approach to diagnosis and therapy is warranted.

3. The below list of presenting symptoms and/or findings (L.O. #2 - “cardinal features”) are tips to specific diagnoses, representing basic illness scripts.
   a. Pain worse with extension in those above middle age with relief upon flexion, with or without associated radiation to lower extremities, fluctuations of pain that are associated with weather changes, aching nature of non-radiating pain, etc., suggest spinal stenosis and associated osteoarthritic changes.
   
   b. When the patient is young and the pain is localized to the back, triggered with extension and lean towards the affected side, and relieved with flexion, a facet dysfunction is suspect.
   
   c. In an athlete participating in a sport that requires repetitive flexion, extension or rotation, LBP associated spasm and tenderness on palpation of the bony posterior elements should alert the clinician that possibility that a pars interarticularis injury exists.
   
   d. Pain that is sharp and burning with radiation to one or both lower extremities in a sciatic nerve distribution, that increases with Valsalva/straining maneuvers, is associated with paresthesias and weakness, and is increased with stretching of the sciatic nerve, is suggestive of radiculopathy (probably from disc herniation). Entrapment of the sciatic nerve by the piriformis muscle (piriformis syndrome) at the sciatic notch can also present like this, except that it does not increase with Valsalva maneuvers and there are no neuropathological symptoms.
   
   e. Sudden onset back pain in older age associated with minimal force suggests osteoporotic related fractures. When there are associated symptoms such as weight loss, fever, chills/sweats, or associated neurological deficits, metastatic or infectious disease of the spine should be suspected.
   
   f. Important features may indicate an underlying infection, malignancy, or urgent/progressive neurologic compromise (e.g. cauda equina syndrome) and are collectively known as “red flags”. These include: history of trauma, Age >50 years, history of cancer of any type, Fevers/chills/night sweats, weight loss >10 pounds in 3 months not directly related to a diet or change in activity (i.e. “unintentional”), recent infection, immunosuppression, pain at rest or at
night, saddle anesthesia, bladder dysfunction (i.e. retention or incontinence, dysuria, hematuria), lower extremity neurologic deficit.

g. Pain localized to the buttock region in an on-off fashion, triggered by twisting movements or lower extremity excursions that is associated with possible leg length discrepancy, or alignment/asymmetry issues can be due to sacroiliac joint dysfunction.

h. LBP associated with diffuse arthralgias/enthesopathies (pain at the entheses or attachment of tendons to bone) may suggest a seronegative spondyloarthropathy (especially if associated with skin, genitourinary or bowel signs and symptoms).

Additional considerations in children
a. A history of psychosocial issues such as peer pressure, family problems (divorce, illness, poverty, etc.) need to be assessed.

b. Children younger than 6 years of age, frequently do not localize pain reliably. Therefore, considering a wide differential diagnosis becomes even more important. Sources of pain that can be referred to the back include the chest (e.g., pneumonia or reflux esophagitis), the abdomen (e.g., appendicitis or pancreatitis), the retroperitoneum (e.g., pyelonephritis-infection of the kidney), or the pelvis (e.g., ovarian cysts).

c. Leukemia (malignancy of leukocytes and their precursors in the blood and bone marrow) may present with bone pain, including back pain.

d. A scoliotic deformity may be a physical sign that is due to back pain as a result of syringomyelia, spine tumor, spondylolisthesis, or herniated nucleus pulposus.

e. In the child with a history of repetitive hyperextension of the spine, such as gymnastics and diving, be suspicious of spondylolysis with acute traumatic pars interarticularis fracture as the cause of low back pain.

f. Nonclassic Scheuermann’s kyphosis (lumbar) can cause low back pain in the child.

g. Intervertebral disc herniation can be a cause of pain in the child with local and locally referred low back pain, with lumbar paraspinal muscle spasm, pain in the buttock, and radiation into the leg.

h. Sacroiliac joint infection in children is uncommon and often difficult to diagnose. It can present with low back pain.

i. Osteoid osteoma and osteoblastoma are benign bone tumors that commonly cause back pain in children.
j. The carrying of backpacks has been associated with low-back pain in children, and this dramatically increases as the child ages.

3. What ancillary studies can you obtain in the evaluation of low back pain and when should these be performed?

**Imaging techniques:**

1. *Radiographs* have little role as a screening tool. In evaluating low back pain, X-rays have their place. In the child with suspicion for a herniated intervertebral disc, plain radiographs are indicated for a complete initial evaluation. In the patient, adult or child, with a history of trauma and suspected instability, obtaining flexion/extension films with the patient lying in the lateral decubitus position may be useful. Severe trauma, suspicion for metastatic disease, rheumatologic conditions, or pars interarticularis injury warrant X-ray examination.

2. *Computed tomography* has little use unless there is the need to rule out obscure fractures/bony pathology. However, CT scanning following myelography is effective in the assessment of lateral recess stenosis.
   
   a. *MRI* is useful in the diagnosis of herniations with high sensitivity. However, MRI has low specificity with abnormalities noted in asymptomatic subjects.


4. *Selective injections* (epidural steroid injections, facet joint and selective nerve blocks): very useful as an adjunct to the H & P. These procedures can also be therapeutic.

5. *Psychological assessment*: pain behavior that is above and beyond what would be expected for the pathological findings should alert the clinician about the existence of psychological overlay to the patient’s symptoms. Non-organic (*Waddel*) signs in the physical examination are suggestive of psychological overlay. These signs include: superficial/non-anatomical distribution of pain, non-anatomic motor/sensory impairment, excessive verbalization of pain or gesturing, production of pain complaints with tests that only simulate specific movements, and inconsistency in pain complaints when the same movement is performed in different positions.

4. What treatment options should be considered for this patient?

**Conservative Treatment:**

1. Shown to be effective: limited bed rest (24-48 hours) in acute LBP; manipulation in acute LBP after spasms have subsided; aerobic exercise; back extensor muscle endurance and strength training; NSAID’s and muscle relaxants in acute LBP with documented spasms.
2. **Equivocal/controversial**: physical therapy exercises; lumbar traction for HNP and radiculopathies; flexibility exercises; rigid mattress; myofascial trigger point injections.
3. **Not yet proven effective**: back class; back supports; manipulation in chronic LBP; work hardening programs.

**Conservative Treatment in Children**

1. Back education in elementary school children has been shown to be efficacious up to 1 year, therefore necessitating ongoing education.
2. Education regarding proper wearing of a backpack and the load carried in the backpack
3. Addressing psychosocial issues: Behavioral therapist, Psychologist, School counselors, and Cognitive therapy. The modalities used include relaxation, distraction, imagery, biofeedback, and self-hypnosis. Also, art or play therapy, family therapy, group therapy, and individual therapy can be effective tools
4. Smoking cessation
5. Weight reduction for those with high BMI
6. Physical modalities to include: physical therapy with an exercise program
7. TENS (transcutaneous electrical nerve stimulation) is a useful noninvasive means of providing pain relief by activating the A-β fibers. When effective, TENS decreases the patient’s pain with virtually no side effects.
8. Acupuncture can be beneficial and works similar to that of TENS (i.e., inhibition of dorsal horn interneurons by activation of A-β fibers.
9. The use of a brace (lumbosacral orthosis) is indicated for 3-4 weeks in the adolescent with acute disk herniation. If pain is severe, bed rest may be indicated for 1-2 weeks. NSAIDs should always be considered.

**Invasive Treatment:**

1. **Spinal injections/blocks**: shown to be effective in selected cases were diagnostic blocks have shown resolution of pain. These techniques include epidural steroid injections, facet blocks, and sacroiliac joint blocks.
2. **Surgical root decompression**: shown to be effective in selected cases with clear-cut radicular/neurogenic pain findings. Most surgeons prefer a round of conservative treatments before surgical options are considered.
3. **Surgical stabilization procedures**: shown to be effective in cases of documented instability.

**Invasive Treatment in Children**

1. Surgical excision is recommended in Osteoid Osteoma and Osteoblastoma to obtain the best relief of pain
2. Surgical disk excision in cases of disk herniation that is resistant to conservative treatment

**Schemas for approach to low back pain: DOD/VA Practice Guidelines**
I. DOD/VA Practice Guidelines for the Management of Low Back Pain in the Adult patient:

1. Evaluate for serious problems by looking for red flags and work-up or refer appropriately:
   - Major trauma
   - Age > 50
   - Persistent fever
   - Hx of cancer
   - Metabolic disorder

   Note: bowel or bladder → *immediate referral to ortho or neurosurgery*

2. Follow the guidance depicted in the following flow charts:
Diagnosis and Management of Low Back Pain
Part I: Screening for Other Health Problems

1. Patient with low back pain/sciatica age > 17 [A]

2. History and physical examination [B]

3. Does the patient have any RED FLAGS?
   - Major trauma
   - Age > 50
   - Persistent fever
   - History of cancer
   - Metabolic disorder
   - M or muscle weakness
   - Bladder or bowel dysfunction
   - Saddle anesthesia
   - Decreased sphincter tone
   - Unrelenting night pain

   Yes 4. Initiate immediate and appropriate action [D]
   No 5. Workup abnormal? Yes 6. Refer/manage as appropriate

7. Does patient have another medical condition presenting as back pain? [E]
   Yes 8. Refer/manager as appropriate
   No 9. Back pain ≤6 weeks? Yes Go to box 10
   No Go to box 22

Go to box 10
Diagnosis and Management of Low Back Pain

Part II: Management of Acute Low Back Pain/Sciatica in Primary Care

Continue from box 9

10 Acute low back pain

11 Consider initiation of one or more of the following conservative treatment options:
1. Education
2. Activity modification
3. Progressive ROM and exercise
4. Symptom control: medications
5. Manipulation
6. Assisted management
7. Bedrest [F]

12 Follow up (visit or phone call) in 1 to 3 weeks as indicated [G]

13 Patient is worse or new neurologic symptoms? Yes

14 Refer/manage as appropriate [H]

15 Patient improved? No

16 * Continue/modify conservative treatment up to 4 to 6 weeks from initial evaluation.
* Consider/modify assisted management and/or work-related ergonomic evaluation. [J]

18 Patient improved? Yes

19 Patient worse? Yes

20 Re-evaluate/go back to box #2 [B] or refer/consult.

21 Pain for > 6 weeks

Go to box 22
Summary:

1. Most LBP is self-limiting.
2. Low back pain is rare in children under 10 years of age, but the incidence increases as the child ages.
3. Previous history of back pain, poor job satisfaction, psychological issues all predispose to chronic LBP.
4. Diagnosis rests primarily on history and physical examination. Diagnostic tests are to be considered adjuncts and supportive of the history and physical examination.
5. Bed rest should be limited to no more than 48 hours in the acute LBP period.
6. Aerobic exercise and back muscle training should be the core of all long-term rehabilitation.
7. Surgery may be warranted in certain cases.
**Practice questions (and answers):**

1. A 72 year old retired Chief presents with a several week history of back pain. If you were considering a diagnosis of prostate cancer and you learned that he has back pain that awakens him from sleep, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely

2. 68 year old retired Colonel presents with a several week history of back pain. If you were considering a diagnosis of osteoporotic fracture and you learned that she had the sudden onset of this pain with no history of trauma, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely

3. A 62 year old retired MSGT with a history of type 2 diabetes mellitus, degenerative joint disease, tobacco abuse and family history of prostate cancer presents with a 2 day history of low back pain. He has not experienced prior episodes of low back pain and states he was watching the Redskins beat the Ravens when his symptoms began. If you were thinking of a diagnosis of osteoarthritis and you found a temperature of 102F on examination, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely

4. A 62 year old retired MSGT with a history of type 2 diabetes mellitus, degenerative joint disease, tobacco abuse and family history of prostate cancer presents with a 2 day history of low back pain. He has not experienced prior episodes of low back pain and states he was watching the Redskins beat the Ravens when his symptoms began. If you were thinking of a diagnosis of multiple myeloma (a malignancy of plasma cells – specific antibody-producing B-lymphocytes – in the bone marrow) and you found that he has a hemoglobin of 8mg/dL, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely
Answers:
1. Much more likely. This is a red flag finding.

2. Much more likely. These are classic/prototypic presentation findings with osteoporotic fracture.

3. Much less likely. Osteoarthritis is NOT associated with inflammatory features such as effusion, swelling, warmth, fever by definition.

4. Much more likely. Low back pain + red flags findings ESPECIALLY when accompanied by new onset of anemia, hypercalcemia, and/or renal failure should suggest multiple myeloma.
ICR Back Pain Cases

The small group cases for this session will be the 3 patients that you will discuss as part of your Integrated Clinical Skills (ICS) experience on this topic.

Please complete the form on the next page for the patient that you wrote up during your ICS session. This form must be turned into your ICR preceptor at the beginning of the ICR small group session on this topic to receive credit.
Name: Session topic: Patient number:

Summary statement (1-3 sentences)

Comprehensive problem list (prioritize by clinical importance)
1.
2.
3.
4.
5.
6.

Prioritized differential diagnosis (include at least 3 diagnostic options)
1.
2.
3.
4.
5.

Justification for leading diagnosis (history and physical exam findings and any ancillary data provided; write as a paragraph. Emphasize data supporting your clinical reasoning):

Plan (diagnostic work-up and/or therapeutic)
1.
2.
3.
4.
INTRODUCTION TO CLINICAL REASONING:
APPENDICULAR ARTHRITIS

Jess D. Edison, MD
William R. Gilliland, MD, MHPE

Objectives
At the end of this session, students will be able to:
1. Define arthritis
2. Distinguish arthritis from mimicking conditions
3. List typical presenting symptoms and physical examination findings for arthritis
4. Compare and contrast inflammatory and non-inflammatory arthritides
5. Construct a differential diagnosis for mono-, oligo- and poly-articular arthritis
6. Describe a general stepwise approach to evaluating arthritis
7. Understand the pathophysiology and key distinguishing features of mono-, oligo- and poly-articular arthritis
8. Understand laboratory (to include synovial fluid analysis) and radiographic work up for common causes of mono-, oligo- and poly-articular arthritis

Overview
This section of the course will discuss a very common presenting problem in medicine. The materials will outline an approach to the diagnosis of arthritis (which is a syndrome) using key findings (history and physical examination findings with typical presentations), heuristics (rules of thumb), mnemonics, and basic illness scripts (basic patterns in presenting symptoms and findings or pattern recognition). The small group cases will also highlight the value of explicitly comparing and contrasting potential diagnoses in the differential, building evidence for and against each diagnosis (i.e. history, physical exam, and laboratory data which supports or does not support that a diagnosis is present); this explicit process is encouraged in this and other courses (i.e. pathology, whereby you need to generate a differential diagnosis). This process can help you identify key findings in a patient’s presentation, weigh the value of individual facts in the presentation, and help you build illness scripts. Let’s start with your first patient before going further.
Your first patient…
A 26-year-old medical student is referred to the outpatient clinic for evaluation of pain in his foot. For 12 weeks, he has had pain and swelling in his left knee and heel. More recently, he has noticed mild pain in his lower back that he attributes to “studying too much and not getting enough sleep.” He has had increasing difficulty making it to his 8 a.m. Human Context course because it is hard to “get himself moving.”

He was quite ill three months ago. He was doing a tropical medicine rotation between his first and second year in Puerto Rico. During that rotation, the health team visited the Dominican Republic and he (and several others) became violently ill with profuse diarrhea, cramps and fevers.

He has had no previous trouble with joints, except for various strains and sprains as a child. All his family members enjoy good health. He is single and shares an apartment near the Grovesnor Metro station with two other medical students. He admits to social drinking, especially on weekends. He is an avowed heterosexual and states that he always uses a condom (“sometimes two”). In the past year, he has had six sexual partners.

He denies having a rash, cough, abdominal pain, chest pain or palpitations. The only other symptoms he mentioned was that his eyes have been red from “pulling several all-nighters”.

Physical examination is remarkable for a healthy-appearing male with a noticeable limp. His general examination is remarkable only for two shallow erosions on his upper palate and a scaly rash on the soles of his feet. His musculoskeletal examination is remarkable for a swollen, warm knee with loss of 30 degrees of flexion. McMurray’s and drawer tests are negative. He has mild swelling at the insertion of his Achilles tendon on his left. His axial skeletal examination is grossly normal although he does have some pain over the dimple of Venus on his right side.

Problem List:
1.
2.
3.
4.
5.
6.
7.
Questions
1) How would you characterize his arthritis?

A. Acute, inflammatory  
B. Acute, non-inflammatory  
C. Chronic, inflammatory  
D. Chronic, non-inflammatory

2) Create a differential diagnosis of possible etiologies of your colleague’s arthritis. Be prepared to defend your choices, specifically mentioning evidence that supports or does not support your diagnoses? (I will help you with the first case. Look at the list of possible etiologies listed below. Pick the top 5 diagnoses that fit the patient’s history and write down information that supports and conflicts with those you have chosen.)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Supporting data</th>
<th>Conflicting data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3) In creating your differential diagnosis, state the significance of the following factors:

1. Age/gender
2. Distribution of joint involvement (knee)
3. Pain over the dimple of Venus
4. Swelling at the insertion of the Achilles tendon
5. Sexual activities
6. Recent travel
7. Negative McMurray’s and drawer tests
8. Scaly rash on soles

You decide to perform the following tests: complete blood count (CBC), erythrocyte sedimentation rate (ESR), stool for fecal leukocytes and occult blood, rheumatoid factor, anti-nuclear antibody, HLA-B27, urethral swab, arthrocentesis, and plain films of his knees, back and feet.

The results are:

**CBC:** WBC 12,300 with normal differential (nl 4,800-10,800); hemoglobin 14.8 gm/dL (nl 14-18 gm/dL); platelet count 340,000 (nl 159,000-400,000)

**ESR:** 30 mm/hr (nl <15 mm/hr)

**RF:** negative  
**ANA:** 1:40 speckled pattern  
**HLA-B27:** negative

**Fecal leukocytes:** negative  
**Fecal occult blood:** negative

**Urethral swab:** a few polys and amorphous pink material, but no organisms on gram stain

**Arthrocentesis:** 40 cc of cloudy fluid obtained from knee with poor viscosity; 43,000 WBCs/mm³ with 85% PMNs; gram stain negative; no crystals; culture is pending


**Radiographs:** all films are unremarkable except effusion in the left knee and soft tissue swelling in the area of insertion of the Achilles tendon

4) **What is the significance of the following results and does it change your differential diagnosis?**

1. Elevated WBC
2. Negative rheumatoid factor
3. Negative HLA-B27
4. ANA of 1:40 titer
5. Urethral smear findings
6. Synovial fluid white count
7. Radiographic findings

5) **What is your final diagnosis?**

6) If the synovial fluid culture is negative, would that change your diagnosis? What about if the urethral smear culture is negative?

7) **What treatment(s) do you recommend?**

**Key Definitions and Distinctions:**
Monoarticular disease often presents acutely and the threat of an infectious etiology is real. By definition, monoarticular syndromes involve only one joint area. In practice, the involvement of 2 or 3 joints may qualify as a monoarticular disease because frequently, the classic monoarticular diseases are actually oligoarticular. **Infection is the most worrisome etiology because it can rapidly destroy a joint in days to weeks.**

Before developing a differential diagnosis for patients presenting with articular complaints, it is important to review key definitions and distinctions to include considering conditions that may mimic an arthritic process. Several conditions may cause inflammation or pain around, but not in the joint. **It is essential that you understand the following terminology which play a pivotal role in helping to establish the diagnosis.**
1. **Arthritis** – Signs of inflammation (erythema, warmth), swelling, crepitus, or loss of range of motion on physical examination
2. **Arthralgias** – Pain in the joint but no signs of swelling, inflammation, or loss of range of motion
3. **Monoarthritis** – One joint involved
4. **Oligoarthritis** (or pauciarticular) – Two to four joints involved
5. **Polyarticular** – Five or more joints involved

**Approach to the Diagnosis Monoarticular Arthritis**

Monoarticular arthritis is a syndrome (constellation of symptoms and findings at the step prior to the diagnosis) but not a diagnosis in and of itself. Defining the syndrome is an important (and extremely helpful) step toward making the diagnosis. However, you are not done with getting to the step of arthritis you need to establish the underlying cause or diagnosis for the arthritis.

In developing your differential diagnosis, there are several important questions to ask.

**Question #1: Is this truly arthritis?**

It is important to recognize arthritis “mimickers” because the treatment and prognosis are often very different from true joint disorders. Examples of mimickers include:

1. Internal derangement
2. Bone pain
3. Neuropathic pain
4. Soft tissue infection
5. Psychiatric illness
6. Tendonitis/bursitis

Several clues (or key findings) on physical examination can help to differentiate between articular and peri-articular pain. *They include differences in pain on range of motion, tenderness, and description of pain.*

<table>
<thead>
<tr>
<th></th>
<th><strong>Intra-articular</strong></th>
<th><strong>Peri-articular</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range of Motion</strong></td>
<td>Pain on passive and active motion</td>
<td>Pain on active and specific motion</td>
</tr>
<tr>
<td><strong>Tenderness</strong></td>
<td>Diffuse</td>
<td>Localized</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Poorly localized</td>
<td>Precisely localized</td>
</tr>
</tbody>
</table>

**Question #2: Is the process acute or chronic?**
In general, rheumatologists use a period of **six weeks** to define chronicity of arthritis. *Acute* = less than 6 weeks; *chronic* = greater than 6 weeks

In **acute** processes, it is helpful to further define the **acuity of onset** of symptoms to help you establish the diagnosis. For example:

1. Seconds to minutes – fracture, internal derangement
2. Hours to days – infection, crystal-induced, inflammatory disorders
3. Days to weeks – indolent infections, osteoarthritis, tumor

**Selected Differential diagnosis of** **monoarticular** arthritis:

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial (septic)</td>
<td>Mycobacterial</td>
</tr>
<tr>
<td>Gout</td>
<td>Lyme arthritis</td>
</tr>
<tr>
<td>Pseudogout</td>
<td>Fungal arthritis</td>
</tr>
<tr>
<td>Trauma (fracture)</td>
<td>Foreign body synovitis</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Early inflammatory disease</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Internal derangement of knee</td>
<td>Pigmented villonodular synovitis</td>
</tr>
</tbody>
</table>

As you may suspect, many polyarticular disorders will start off with one or a few joints involved. The following oligoarticular or polyarticular disorders frequently start off as a **monoarticular disease**.

- Rheumatoid arthritis
- Juvenile rheumatoid arthritis
- Enteropathic arthritis
- Reiter’s Syndrome (Reactive arthritis)
- Whipple’s disease
- Psoriatic arthritis
- Viral arthritis
- Sarcoidosis

**Question #3: Is the process inflammatory or non-inflammatory?**

Characteristics of an **inflammatory** condition:

1. Protracted morning stiffness (greater than 30 minutes)
2. Constitutional symptoms (i.e., fevers or night sweats)
3. Signs of inflammation on physical exam (i.e. erythema, warmth, tenderness)
4. Synovial fluid white blood cell count (WBC) greater than 2,000 cells/mm³

**Most of the conditions in the above differential diagnosis are inflammatory but several are not.** Non-inflammatory monoarticular processes include trauma, hemarthrosis, pigmented villonodular synovitis (PVNS), mechanical derangements, and osteoarthritis.
Question #4: What are the demographics of the patient? (What is the patient at risk for?)

With the exception of infection (which may occur in all ages), some joint diseases presenting as monoarthritis typically occur in certain age groups.

**Children** – Bacterial infection, juvenile rheumatoid arthritis, hip dysplasia, slipped capital femoral epiphysis. This demographic is unlikely to have crystal-induced disease.

**Young adults** – Gonococcal arthritis, seronegative spondyloarthropathy, rheumatoid arthritis, internal derangement of the knee. May have crystal-induced disease such as gout, but unusual.

**Older adults** – Crystal-induced disease, osteoarthritis, avascular necrosis, internal derangement, systemic inflammatory diseases.

Question #5: Which joint (or joints) is (are) involved?

Certain diseases have a propensity to affect certain joints. As an example, gout commonly affects the first metatarsal-phalangeal joint (MTP). When the first MTP is inflamed, we refer to it as podagra. Other typical joints affected in association with specific diseases include:

**First carpometacarpal** – osteoarthritis

**Distal interphalangeal joints of the hands** – osteoarthritis, psoriatic arthritis

**Wrist** – gonococcal arthritis, early inflammatory diseases

**First metatarsophalangeal** – gout, osteoarthritis

**Knee** – bacterial arthritis, juvenile rheumatoid arthritis, osteoarthritis, pseudogout, internal derangement, hemarthrosis, rheumatoid arthritis, reactive arthritis, Lyme arthritis

**Ankle** – sarcoidosis, Reiter’s syndrome (reactive arthritis)

Question #6: Are there extra-articular (systemic) features?

*Systemic features can be very helpful, but also misleading.* Fever is often associated with an infectious arthritis, but it is not universally present. On the other hand, fevers may be associated with many other arthritic processes to include gout, pseudogout, sarcoidosis, juvenile rheumatoid arthritis, etc. Remember: **There are few absolutes in medicine!**

With that being said, listed below are some useful extra-articular (systemic) associations.

**Fevers** – bacterial, viral, gout, reactive arthritis, systemic inflammatory disorders, sarcoidosis

**Ocular** – juvenile rheumatoid arthritis, Reiter’s, sarcoidosis

**Gastrointestinal** – Crohn’s disease, ulcerative colitis, celiac disease, other enteropathic arthritis

**Respiratory** – sarcoidosis, tuberculosis, rheumatoid arthritis, systemic lupus erythematosus
**Nervous system** – meningococcal, Lyme, systemic lupus erythematosus

**Rashes** – systemic lupus erythematosus, Lyme, psoriasis, gonorrhea, Reiter’s, sarcoidosis

**Question #7: What is an appropriate initial work-up for an acute monoarthritis?**

The critical diagnosis to consider is **joint infection (septic arthritis)**. Bacterial infections can destroy a joint in a matter of days, so prompt and proper treatment will decrease the likelihood of significant joint damage. Therefore, it should come as no surprise that **arthrocentesis** is the most important test, especially in acute monoarticular presentations!

**Arthrocentesis** – Send fluid for cell count, culture, and evaluation for crystals.

If you suspect gonorrhea, assure that the fluid is plated on the appropriate medium either at the bedside or by the laboratory. Use chocolate agar for synovial fluid (all sterile sites) and Thayer-Martin for all “dirty” or non-sterile sites (cervical, urethral, pharyngeal, or rectal).

In non-gonococcal septic arthritis, cultures are positive in approximately 100% of cases, and gram stains show bacteria in 75% of gram-positive organisms and 50% of gram-negative organisms.

**Radiographs of the joint and the contralateral joint** – Although frequently normal, the radiograph may reveal important information, especially in cases of suspected fracture or infection. The contralateral film serves as a basis for comparison.

**Routine blood tests** – Complete blood count, blood cultures, and cultures of other suspected sources of infection are the most helpful. Measurements of acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may help to distinguish between an inflammatory and non-inflammatory process. Anti-nuclear antibody (ANA), rheumatoid factor, and uric acid levels are not particularly helpful in this setting.

**Question #8: What synovial fluid features help to distinguish between inflammatory and non-inflammatory diseases?**

<table>
<thead>
<tr>
<th>Type of fluid</th>
<th>Appearance</th>
<th>Leukocytes/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear, colorless, viscous</td>
<td>&lt;200 (&lt;10% PMNs)</td>
</tr>
<tr>
<td>Non-inflammatory</td>
<td>Clear, colorless, viscous</td>
<td>200-2,000 (&lt;25% PMNs)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Cloudy, yellow, watery, low</td>
<td>2,000-50,000 (&gt;50%)</td>
</tr>
<tr>
<td></td>
<td>glucose</td>
<td>PMNs)</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>Septic</td>
<td>Purulent, very low glucose</td>
<td>&gt;80,000 (&gt;75% PMNs)</td>
</tr>
</tbody>
</table>

Note: The conventional wisdom to consider effusions containing greater than 80,000 WBCs/mm³ as septic is a guideline, not a strict rule. Other diseases, notably gout, Reiter’s (reactive arthritis), etc., may also present with markedly elevated WBC counts.

Question #9: Are crystals present?

Crystal-induced diseases generally present with an acute onset of an intensely inflamed joint that may be confused with an infection. A specimen of joint fluid should be promptly examined with a polarized light microscope. A drop of synovial fluid is placed on a clean microscope slide and covered with a cover slip. It is then evaluated under ordinary light microscopy and then under a polarized microscope using a first-order red compensator. While the presence of crystals is very suggestive of crystal-induced disease, they do not exclude infection. Hints for remembering the differences between urate and calcium pyrophosphate crystals are listed below:

<table>
<thead>
<tr>
<th></th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape</strong></td>
<td>Needle</td>
<td>Rhomboid</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>1-2 WBCs</td>
<td>Less than 1 WBCs</td>
</tr>
<tr>
<td><strong>Birefringence</strong></td>
<td>Negative (strong)</td>
<td>Positive (weak)</td>
</tr>
<tr>
<td><strong>Color when parallel to axis</strong></td>
<td>Yellow</td>
<td>Blue</td>
</tr>
</tbody>
</table>

Mnemonic:
ABC – Aligned, Blue, Calcium
PYG – Parallel, Yellow, Gout

Question #10: How can you differentiate between gonococcal and non-gonococcal arthritis?

They are very different disorders, but the following epidemiologic, clinical and prognostic differences are helpful to distinguish between the two:

<table>
<thead>
<tr>
<th>Features</th>
<th>Non-gonococcal</th>
<th>Gonococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>Very young and old, immunocompromised, ill</td>
<td>Young adults, healthy, sexually active</td>
</tr>
<tr>
<td>Initial symptoms</td>
<td>Monoarthritis</td>
<td>Migratory, polyarthritis</td>
</tr>
<tr>
<td>Rash</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Question #11: What is the appropriate work-up for chronic monoarticular arthritis?

In chronic monoarticular disease, the differential shifts away from some important causes in the acute setting (i.e. pyogenic and crystal-induced disease). In patients with an...
inflammatory synovial fluid, the likelihood of chronic inflammatory conditions such as a seronegative spondyloarthropathy, fungal infection and mycobacterial infection increases.

**Radiographs of the joint** – Although frequently normal in acute processes, they are often revealing in chronic processes. Chronic infections by mycobacteria and fungi often cause radiographic abnormalities. Osteoarthritis, avascular necrosis, and other causes of non-inflammatory chronic arthritis may also have characteristic changes.

**Arthrocentesis** – This is extremely helpful in dividing possible causes of inflammatory and non-inflammatory causes. Cultures of the fluid may demonstrate mycobacterial or fungal infection, but you must tell the labs you are considering such organisms. The presence of bloody fluid may indicate pigmented villonodular synovitis, hemarthrosis or synovial chondromatosis.

If tuberculosis is a consideration, synovial fluid smears for mycobacterium are positive in 20%, cultures are positive in 80% and synovial biopsy with culture is positive in >90%.

**Routine blood tests** – Serologic tests for Lyme disease, rheumatoid factors, and anti-nuclear antibodies are more helpful in cases of chronic arthritis. Acute phase reactants may also help to distinguish between an inflammatory and non-inflammatory process.

**Other lab tests to consider in selected patients:**
- **Radiographs of the sacroiliac joints** – In order to demonstrate sacroiliitis in a young male with chronic arthritis
- **Chest radiograph** – To detect evidence of tuberculosis or sarcoidosis
- **Tuberculin skin test** – A negative test is useful to exclude tuberculosis
- **Synovial biopsy** – Helpful in diagnosing tumors, foreign-body synovitis, fungal and mycobacterial infections, sarcoidosis, and pigmented villonodular synovitis
- **MRI** – Useful in diagnosing internal derangements, osteomyelitis, avascular necrosis and early erosions
- **Arthroscopy** – Useful in obtaining more synovial tissue for studies and diagnosing internal derangements

**Returning to our patient..........(key features are in bold)....**
Your patient, a 26-year-old medical student, is referred to the outpatient clinic for evaluation of pain in his foot. For 12 weeks, he has had pain and swelling in his left knee and heel. More recently, he has noticed mild pain in his lower back that he attributes to “studying too much and not getting enough sleep.” He has had increasing difficulty making it to his 8 a.m. Human Context course because it is hard to “get myself moving.”

He was quite ill three months ago. He was doing a tropical medicine rotation between his first and second year in Puerto Rico. During that rotation, the health team visited the
Dominican Republic and he (and several others) became violently ill with profuse diarrhea, cramps and fevers.

He has had no previous trouble with joints, except for various strains and sprains as a child. All his family members enjoy good health. He is single and shares an apartment near the Grovesnor Metro station with two other medical students. He admits to social drinking, especially on weekends. He is an avowed heterosexual and states that he always uses a condom (“sometimes two”). In the past year, he has had six sexual partners.

He denies having a rash, cough, abdominal pain, chest pain or palpitations. The only other symptoms he mentioned was that his eyes have been red from “pulling several all-nighters”.

Physical examination is remarkable for a healthy-appearing male with a noticeable limp. His general examination is remarkable only for two shallow erosions on his upper palate and a scaly rash on the soles of his feet. His musculoskeletal examination is remarkable for a swollen, warm knee with loss of 30 degrees of flexion. McMurray’s and drawer tests are negative. He has mild swelling at the insertion of his Achilles tendon on his left. His axial skeletal examination is grossly normal although he does have some pain over the dimple of Venus on his right side.

| 1. 12 weeks of foot pain with swelling in the heel at the insertion of the Achilles tendon. |
| 2. Knee synovitis with decreased range of motion on examination. |
| 3. Low back pain and morning stiffness with pain on palpation of the right “Dimple of Venus”. |
| 4. A history of recent diarrheal illness. |
| 5. A history of six recent sexual partners. |
| 6. Red eyes. |
| 7. Erosions on the hard palate. |
| 8. Scaly rash on the soles of his feet. |

**Question #1**
How would you characterize his arthritis?

A. Acute, inflammatory
B. Acute, non-inflammatory
C. Chronic, inflammatory
D. Chronic, non-inflammatory

**Question #2**
Create a differential diagnosis of possible etiologies of your colleague’s arthritis. Be prepared to defend your choices, specifically mentioning evidence that supports or does not support your diagnoses? (I will help you with the first case. Look at the list of possible etiologies listed below. Pick the top 5 diagnoses that fit the patient’s history and write down information that supports and conflicts with those you have chosen.)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Supporting data</th>
<th>Conflicting data</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Enteropathic arthritis</td>
<td>Chronic large joint monoarticular arthritis with inflammatory low back pain</td>
<td>- No known history of inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The rash is not an ulcerative pyoderma gangrenosum</td>
</tr>
<tr>
<td>B. Parvovirus arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. HIV-related arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. <strong>Gonococcal arthritis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. Ankylosing spondylitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. Rheumatoid arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G. Tuberculous arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. Sarcoidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Lyme arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. <strong>Systemic lupus erythematosus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. Gout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. <strong>Reiter’s syndrome/reactive arthritis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Psoriatic arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. Osteoarthritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Enteropathic arthritis
   - Chronic large joint monoarticular arthritis with inflammatory low back pain
   - No known history of inflammatory bowel disease
   - The rash is not an ulcerative pyoderma gangrenosum

2. Gonococcal arthritis
   - Young sexually active patient with inflammatory arthritis and tenosynovitis
   - The rash is not hemorrhagic macular papular dermatitis
   - Diarrhea as opposed to urethritis

3. Systemic lupus erythematosus
   - Young patient with chronic inflammatory arthritis, palatal erosion and inflammatory eye disease
   - This is not a malar or discoid rash
   - Lacks pleurisy, nephritis, neurologic disease
   - Inflammatory low back pain not common
   - Does not typically follow a diarrheal illness

4. Reiter’s syndrome/reactive arthritis
   - Preceding diarrheal illness
   - Chronic inflammatory oligoarticular arthritis
   - Sacroiliitis
- Uveitis
- Enthesopathy
- Keratoderma blenorrhagica

5. Psoriatic arthritis
Chronic inflammatory arthritis
- The rash is not psoriatic
- Does not typically follow a diarrheal illness

Question #3
In creating your differential diagnosis, state the significance of the following factors:

1. Age/gender: Demographics are helpful as they can provide clues to a diagnosis, i.e. systemic lupus erythematosus is most commonly seen in young African-American females.

2. Distribution of joint involvement (knee): This is an important feature although the knee can be involved in many inflammatory joint diseases to include all seronegative spondyloarthropathies (Reiter’s syndrome/reactive arthritis, psoriatic arthritis, enteropathic arthritis, ankylosing spondylitis). The knee will typically be involved in gonococal arthritis and can be seen with systemic lupus erythematosus.

3. Pain over the dimple of Venus: This finding suggests sacroiliitis which is commonly seen in the seronegative spondyloarthropathies.

4. Swelling at the insertion of the Achilles tendon: This is enthesopathy, a common finding in seronegative spondyloarthropathies.

5. Sexual activities: This is a very important feature as it may suggest gonococcal arthritis or Reiter’s syndrome/reactive arthritis secondary to Chlamydia.

6. Recent travel: This in combination with a preceding diarrheal syndrome is a strong clue in the scenario as it would suggest Reiter’s syndrome/reactive arthritis.

7. Negative McMurray’s and drawer tests: This is a distracter.

8. Scaly rash on soles: If you know what the rash is then it is a potential give away and is very important in narrowing your differential if not giving the diagnosis. This should not be confused with psoriasis.

You decide to perform the following tests: complete blood count (CBC), erythrocyte sedimentation rate (ESR), stool for fecal leukocytes and occult blood, rheumatoid factor,
anti-nuclear antibody, HLA-B27, urethral swab, arthrocentesis, and plain films of his knees, back and feet.

The results are:

- **CBC**: WBC 12,300 with normal differential (nl 4,800-10,800); hemoglobin 14.8 gm/dL (nl 14-18 gm/dL); platelet count 340,000 (nl 159,000-400,000)
- **ESR**: 30 mm/hr (nl <15 mm/hr)
- **RF**: negative
- **ANA**: 1:40 speckled pattern
- **HLA-B27**: negative
- **Fecal leukocytes**: negative
- **Fecal occult blood**: negative
- **Urethral swab**: a few PMNs and amorphous pink material, but no organisms on gram stain
- **Arthrocentesis**: 40 cc of cloudy fluid obtained from knee with poor viscosity; 43,000 WBCs/mm³ with 85% PMNs; gram stain negative; no crystals; culture is pending
- **Radiographs**: all films are unremarkable except effusion in the left knee and soft tissue swelling in the area of insertion of the Achilles tendon

**Question #4**

What is the significance of the following results and does it change your differential diagnosis?

1. Elevated WBC: Helpful in suggesting an active inflammatory disease but is not specific.
2. Negative rheumatoid factor: Helpful as it goes along with a seronegative spondyloarthritis.
3. Negative HLA-B27: Although we might like to see a positive HLA-B27, it is not a diagnostic test and is not always positive in seronegative spondyloarthritis.
4. ANA of 1:40 titer: Nonspecific.
5. Urethral smear findings: Very helpful as we suspect to see sterile pyuria with Reiter’s syndrome/reactive arthritis.
7. Radiographic findings: Helpful but nonspecific.

**Question #5**

What is your final diagnosis? Reactive arthritis, sexual associated, once referred to as Reiter’s Syndrome.
Question #6
If the synovial fluid culture is negative, would that change your diagnosis? What about if the urethral smear culture is negative? Negative cultures are actually what we are looking for as they suggest a reactive component as opposed to a septic arthritis.

Question #7
What treatment(s) do you recommend? I would try a localized injection of corticosteroids and non-steroidal anti-inflammatory drugs as first line therapy

APPENDICULAR ARTHRITIS

An Approach to the Differential Diagnosis of Polyarticular Arthritis

The history and physical examination is especially helpful in the differential diagnosis of polyarticular arthritis. An inexperienced physician may often slight the history and physical and “shotgun” laboratory testing to establish a diagnosis. While rheumatoid factors, anti-nuclear antibodies, ASO titers, etc. may be helpful, the history and physical examination will reveal 75% of the information required for diagnosis.

No single classification scheme can be used to differentiate the wide variety of diseases that may present with polyarticular disease. Many clinicians use a series of factors that will help sort out the diagnostic possibilities. These include:

- Acuteness of onset
- Presence of systemic symptoms
- Degree of inflammation
- Distribution of joint involvement
- Age and sex of patient

Like the prior note set on monoarticular arthritis, this note set will help you create a differential diagnosis using a series of questions.

Question #1: Is this truly arthritis?

Although the following are less likely to be confused with chronic conditions than acute conditions, remember that these conditions that can mimic arthritis.

1. Internal derangements
2. Bone pain
3. Neuropathic pain
4. Soft tissue infection
5. Psychiatric illness
6. Tendonitis/bursitis
**Polyarthritis** refers to the presence of inflammation (swelling, tenderness and/or warmth) in 5 or more joints. **Polyarthralgia** refers to pain without demonstrable inflammation in 5 or more joints.

**Question #2: Is the process acute or chronic?**

Remember that chronic is arbitrarily defined as any process that lasts longer than 6 weeks. Think in terms of “geologic time” when evaluating chronic polyarticular diseases. Why?

1. The disease may present very insidiously.
2. It may masquerade as other diseases until it becomes more classic in appearance.
3. Characteristic laboratory abnormalities may take months to years to develop.
4. Joint symptoms may precede extra-articular features of the disease by months to years.
5. Radiographs may be normal.

**Question #3: Is the process inflammatory or non-inflammatory?**

Characteristics of an inflammatory condition include:

1. Constitutional symptoms
2. Signs of inflammation on examination (erythema, warmth)
3. Synovial fluid white blood count (WBC) greater than 2,000 cells/mm³
4. Protracted morning stiffness

Just by answering the first 3 questions, you can create a preliminary differential diagnosis!

<table>
<thead>
<tr>
<th>Acute Inflammatory</th>
<th>Infections – gonococcal, meningococcal, Lyme, acute rheumatic fever, bacterial endocarditis, viral (parvovirus, rubella, hepatitis B, Epstein-Barr, HIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Other inflammatory</strong> – polyarticular gout, sarcoid arthritis, serum sickness, any early inflammatory disease (rheumatoid arthritis, Reiter’s/reactive arthritis, etc.)</td>
</tr>
<tr>
<td>Acute Non-Inflammatory</td>
<td><strong>Unusual</strong> – acute presentation of OA (?)</td>
</tr>
<tr>
<td>Chronic Inflammatory</td>
<td><strong>“Classic” rheumatic diseases</strong> – rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), polymyositis, scleroderma, Reiter’s syndrome/reactive arthritis, psoriatic arthritis, enteropathic arthritis, vasculitis, polymyalgia rheumatica</td>
</tr>
</tbody>
</table>
**Chronic Non-Inflammatory**

Osteoarthritis, Paget’s disease, fibromyalgia, benign hypermobility syndrome, inherited disorders of collagen (Ehlers Danlos), hemochromatosis

**Question #4: Is there any particular pattern of joint involvement?**

**Migratory** – Symptoms are present in certain joints for a few days and then remit, only to appear in other joints. Examples: rheumatic fever, gonococcal arthritis, early phase of Lyme disease.

**Additive** – Symptoms begin in some joints and persist, with subsequent involvement of other joints. Examples: rheumatoid arthritis, SLE.

**Intermittent (palindromic)** – Repetitive attacks of polyarthritis with complete remission in between attacks. Examples: palindromic rheumatism, polyarticular gout, Reiter’s syndrome, sarcoidosis.

**Question #5: Which joints are involved?**

Different diseases affect different joints. Knowledge of the typical joints involved is the cornerstone of diagnosing a polyarticular disease.

**Distribution of Joint Involvement in Polyarthritis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Joints/Articulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Wrist, PIPs, MCPs, elbows, shoulders, cervical spine, hips, knees, MTPs, ankles</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>First CMC, DIPs, PIPs, cervical spine, lumbar spine, hips, knees, first MTP</td>
</tr>
<tr>
<td>Systemic lupus erythematous</td>
<td>Wrist, PIPs, MCPs, elbows, shoulders, MTPs, ankles, feet</td>
</tr>
<tr>
<td>Gonococcal arthritis</td>
<td>Knee, wrist, ankle, hand IPs</td>
</tr>
<tr>
<td>Reiter’s syndrome/ reactive arthritis</td>
<td>Knee, ankle, MTP, toe IPs, elbow, axial spine</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Knee, ankle, MTP, toe IPs, wrists, MCPs, hand IPs, axial spine</td>
</tr>
<tr>
<td>Enteropathic arthritis</td>
<td>Knee, ankle, elbow, shoulder, MCPs, PIPs, wrist, axial spine</td>
</tr>
<tr>
<td>Polyarticular gout</td>
<td>First MTP, instep, heel, ankle, knee</td>
</tr>
<tr>
<td>CPPD disease</td>
<td>Knee, wrist, shoulder, ankle, MCPs, hand IPs, hip, elbow</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Ankle, knee</td>
</tr>
</tbody>
</table>


**Question #6: What are the demographics of the patient?**
The age and gender of the patient has a profound influence on likely diagnoses in a given patient. For example, it would be unusual for a 90-year-old male to present with gonococcal arthritis (but possible!), while it may be very likely in a 20-year-old male.

**Influence of Age and Gender on the Differential Diagnosis of a Chronic Polyarthritis**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Likely Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young women (age 25-50)</td>
<td>Osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, gonococcal arthritis, fibromyalgia, hypermobility syndrome</td>
</tr>
<tr>
<td>Young men (age 25-50)</td>
<td>Gonococcal arthritis, Reiter’s syndrome/reactive arthritis, ankylosing spondylitis, osteoarthritis, hemochromatosis</td>
</tr>
<tr>
<td>Patients greater than 50</td>
<td>Osteoarthritis, rheumatoid arthritis, calcium pyrophosphate disease, (CPPD), polymyalgia rheumatica, paraneoplastic</td>
</tr>
</tbody>
</table>

**Question #7: Are there systemic features?**

The presence or absence of systemic features is especially useful in the differential diagnosis of polyarthritis. Certain diagnoses may be associated with specific rashes (i.e. erythema marginatum with acute rheumatic fever). Although few are specific, the following systemic features may provide useful information in making the correct diagnosis.

**Morning stiffness:** The amount of time it takes to “limber up” in the morning. In many cases of inflammatory arthritis, it generally takes more than 30 minutes.

**Fevers:** Infections – septic arthritis, bacterial endocarditis, viral arthritis, Lyme arthritis, tuberculosis

  Reactive arthritis – Reiter’s syndrome, rheumatic fever, inflammatory bowel disease

  Systemic inflammatory diseases – rheumatoid arthritis, Still’s disease, vasculitis, SLE

  Crystal-induced – gout, pseudogout

  Miscellaneous – Kawasaki’s, sarcoidosis, malignancy, Henoch-Schonlein purpura

**Rash:** Lyme disease – erythema chronicum migrans

  Sarcoidosis, enteric disease – erythema nodosum

  Psoriasis – psoriatic plaques

  Reiter’s/reactive arthritis – keratoderma blennorrhagicum

  Systemic lupus – malar rash, photosensitivity, discoid lesions

  Dermatomyositis – Gottron’s sign/papules, heliotrope rash

**Raynaud’s:**

  Progressive systemic sclerosis (90%)

  Systemic lupus erythematosus (20%)
Polymyositis/dermatomyositis (20-40%)

Others:
Lung – rheumatoid arthritis, sarcoidosis, SLE, progressive systemic sclerosis
Pleura – SLE, progressive systemic sclerosis, polymyositis/dermatomyositis, rheumatic fever
Pericardium – rheumatic fever, SLE, rheumatoid arthritis, polymyositis/dermatomyositis
Heart valve – SLE, rheumatic fever, endocarditis, rheumatoid arthritis
Kidney – SLE, gout, endocarditis, serum sickness, progressive systemic sclerosis
GI tract – inflammatory bowel disease, progressive systemic sclerosis, vasculitis
Liver – rheumatic fever, progressive systemic sclerosis, sarcoidosis, polymyalgia rheumatica, hemochromatosis

Question #8: What is an appropriate work-up for a chronic polyarthritis?

The work-up for polyarticular disease is often quite different from monoarticular diseases we mentioned earlier. In monoarticular processes, arthrocentesis is the most important test because we worry about infection or crystal-induced disease. While arthrocentesis is still important, radiographs and blood tests are often more important (after history and physical) in the evaluation of chronic polyarthritis.

Routine blood tests – Next year, you will learn more about the “rheumatology panel”. The following tests are useful in evaluating patients with chronic arthritis:
- Anti-nuclear antibody (ANA)
- Erythrocyte sedimentation rate (ESR)
- Complete blood count (CBC)
- Rheumatoid factor
- Liver enzymes
- Chemistry panels

BUT know the limitations of these tests! They rarely make a diagnosis by themselves and should be used with other clinical data to make the diagnosis. Many inflammatory processes in the acute setting may present with positive ANAs and rheumatoid factor which have little clinical utility.

Other tests that may be helpful in the “right” clinical setting include:
- Thyroid stimulating hormone (TSH)
- Iron studies
- Synovial fluid analysis
- Lyme titer
- Parvovirus, ASO and DNase-B titers

Radiographs – As a rule, patients with acute polyarticular diseases will not benefit from radiographs. On the other hand, radiographs are very helpful in evaluating chronic conditions which may have characteristic changes in the joints. Osteoarthritis,
rheumatoid arthritis, gout, and sarcoidosis are examples of diseases with characteristic changes on radiographs.

**Arthrocentesis** – When the diagnosis has not been established and joint fluid can be obtained, then aspiration may be helpful. A patient with obvious osteoarthritis who has a small knee effusion probably doesn’t require a diagnostic arthrocentesis. If a crystal-induced or infectious disease is considered, arthrocentesis can be useful in ruling them out. However, note that many diseases listed in the differential diagnosis of a chronic polyarticular disease will have “inflammatory” fluid.

**Your next patient…..arthritis in children**

You are seeing a 7 year old male who is complaining of right thigh pain for the past five days. He also has a limp. He is otherwise healthy, but did have an upper respiratory infection two weeks ago that resolved without any complications. He does not report any fevers with this pain or with his previous cold. He denies any trauma and notes that his pain is progressively getting worse. He denies rashes, vomiting, diarrhea, and has no family history of joint problems. On physical exam, he has limited range of motion, specifically with abduction and internal rotation of his right hip. His right thigh is non-tender and his right knee is without swelling and has full range of motion. The rest of his exam is unremarkable.

The initial approach to the evaluation of a child with arthritis includes a detailed history and physical exam. Characterizing the pain can be difficult for children, so the clinician can ask about changes in activity level as well as night waking from pain, both of which are important distinguishing features. Often, in toddlers, a history of trauma may be hard to ascertain since they fall so frequently. Obtaining a thorough review of systems including other systemic symptoms such as fever, fatigue, rashes, weight loss, or abdominal pain will help establish the diagnosis as well.

Children often complain of pain in their extremities. The presence of a true arthritis on physical exam requires a more urgent evaluation. Arthralgia, on the other hand, which refers to pain around a particular joint, is a more common, often self-resolving issue that can be caused by a systemic viral infection, overuse injuries, or growing pains. Determining if the arthritis is acute or chronic, which joints are affected, and performing an age-sensitive musculoskeletal exam to include inspection, palpation, and range of motion helps determine what further diagnostic studies might be indicated. Arthritis can be the presenting manifestation for any of the rheumatic diseases of childhood, including juvenile idiopathic arthritis or JIA (formally called JRA, or juvenile rheumatoid arthritis), systemic lupus erythematosus (SLE), juvenile dermatomyositis, sarcoidosis, and the vasculitic syndromes such as Henoch-Schonlein Purpura (HSP).

In addition, arthritis in children can be caused by an infectious process or a post-infectious complication. Joint pain and swelling of a single joint suggests trauma or infection. Acute bacterial infection of the joint space can lead to arthritis and is usually referred to as a “septic joint.” A “reactive arthritis” is inflammation at one or more joints that is distant from the site of infection and occurs 1-3 weeks after an inciting infection. Reactive arthritis has been associated with previous gastrointestinal infections (Salmonella, Shigella, Campylobacter, or Yersina), sexually transmitted infections, and
group A streptococcal infections. Acute rheumatic fever (ARF) is characterized by exquisite joint pain and tenderness, a persistent fever, and polyarthritis that is usually migratory. Lyme disease should also be considered in children living in or visiting endemic areas who present with oligoarthritis. These infections have a sterile synovial fluid, unlike a septic joint, in which bacteria typically grows.

In addition, “toxic synovitis” is a transient inflammation of a joint and is the most common cause of hip pain in children. It typically affects children 4 to 10 years old and is twice as common in boys. A previous upper respiratory infection is a common finding on history.

In patients with acute, monoarticular arthritis, a plain film is helpful to rule out a fracture, avascular necrosis, or bone tumors. A “septic joint” should be aspirated for diagnostic as well as therapeutic benefit. Most often, however, the arthritis is due a post-infectious inflammatory process, or “reactive arthritis”, that is less severe in presentation, and requires simply pain control and reassurance. In patients with more chronic (weeks to months) oligoarthritis or polyarthritis, labs should be obtained to evaluate for autoimmune disorders (SLE, HSP, JIA).

You decide to send the patient for a plain film. It is common for hip pain to be referred to the thigh and even the groin in children this age. You are concerned about either a transient reactive arthritis versus a septic arthritis. The x-ray is normal. Since you are concerned about an effusion, you obtain an ultrasound of the hip which reveals a joint effusion. On consultation with the pediatric orthopedic surgeon, you decide to obtain some fluid by aspirating the joint. Your patient feels much better after the procedure and the fluid analysis is clear, without signs of an acute bacterial infection. The patient is treated with anti-inflammatory medication and rest until his pain subsides over the next week.
Practice questions (and answers):

1) A 35 year old elementary school teacher presents to your outpatient clinic with complaints of 4 weeks of hand stiffness and pain in all of her metacarpophalangeal joints (MCP’s) and proximal interphalangeal joints (PIP’s). The stiffness lasts most of the day and she has noticed swelling at these joints and has difficulty making a fist. Her symptoms began rather suddenly over the course of a few days. She has no other associated symptoms. In the course of your interview she relates that a number of children at her school have been sick with an illness that manifests as a rash that gives them a “slapped cheek” appearance. You suspect that this may represent a viral arthritis, likely parvovirus B-19. How would you classify this arthritis?

   A) Chronic oligoarticular
   B) Chronic polyarticular
   C) Acute polyarticular
   D) Acute oligoarticular

2) A 65 year old white female presents for evaluation of hand pain of many years duration. She reports the gradual onset of pain in her distal interphalangeal joints (DIP) and 1st carpal metacarpal (CMC) joints. The pain is made worse with activity, specifically knitting. She reports morning stiffness which lasts 15-20 minutes as well as stiffness after periods of inactivity. She does not recall any swelling. She has been evaluated in the past and has radiographs which reveal asymmetric joint space loss in the DIP’s and 1st CMC with osteophyte formation, subchondral sclerosis, and some central erosions leaving a “gull wing” pattern at the DIP’s. She reports modest symptom relief with Tylenol 1gm three times daily, but has returned to clinic to see if there are any new treatment modalities. Examination reveals loss of active and passive range of motion at the DIP joints. She has firm nodular masses at her DIP joints which you feel are consistent with Heberden’s nodes. There is no palpable synovitis. Examination of her nails reveals no pits. Her skin examination reveals no rashes. Heart and lung examination is unremarkable. How would you classify this disease process?

   A) Chronic non-inflammatory poly arthritis
   B) Chronic inflammatory oligoarthritis
   C) Acute non-inflammatory oligoarthritis
   D) Acute inflammatory oligoarthritis

3) What is the most likely diagnosis?

   A) Psoriatic arthritis
   B) Rheumatoid arthritis
   C) Osteoarthritis
   D) Gout

4) A 67 year old Caucasian male presents to the emergency department with a chief complaint of sudden onset right knee swelling and pain which began 24 hours ago. He does not recall any falls or injuries. He has a known history of chronic kidney disease, mild congestive heart failure, hypertension, and hyperlipidemia. The pain is described as
intense, ten out of ten, and woke him from sleep yesterday morning. He reports feeling feverish in the past 24 hours, but has not noted any rigors. He has been unable to walk and is in a wheelchair. The knee is red, visibly swollen, and warm to the touch. Range of motion testing and further examination is limited by pain. What is the next best course of action?

A) Weight bearing radiographs of the knees  
B) IV administration of vancomycin 30mg/kg every 12 hours  
C) Arthrocentesis with synovial fluid analysis for crystals, cell count, and culture  
D) Laboratory evaluation with complete blood count, erythrocyte sedimentation rate, uric acid, and complete metabolic panel.

5) A 24 year Hispanic female Active Duty E-4 returned from a 15 month deployment to Iraq a few weeks ago and presents for evaluation of hand pain and fatigue which began three months prior to her re-deployment. While deployed, she worked in the motor pool and spent a significant amount of time during the day outside in the sun. Her friends in the unit noticed that she seemed to get “sunburned” easily, but she did not think much of it. She has had progressively worsening fatigue and hand pain and had to get a temporary profile from her brigade surgeon because she could not complete the APFT. She has noticed it is difficult to hold wrenches and she is frequently dropping bolts and other parts. Her past medical history is unremarkable and family history is negative. Her examination is remarkable for an erythematous rash on her cheeks which spans the bridge of her nose. You also notice an ulcer on her hard palate which she describes as non-painful. Heart sounds are regular and you don’t notice any murmurs. Lungs are clear. Her musculoskeletal examination is remarkable for her inability to make a complete fist due to diffuse swelling at her MCP and PIP joints on both hands. On palpation of these joints you feel boggy synovial tissue and she reports the exam is mildly painful. You suspect this patient has an autoimmune connective tissue disease. What set of laboratory tests listed below is most specific for systemic lupus erythematosus.

A) ESR – 68 mm/hr (0-22mm/hr)  
B) RF – 216 (0-24IU/ml), CCP 189  
C) ANA 1:640 (greater than 1:40 is abnormal)  
D) Positive Smith antibody

6) A 31 year old Army Specialist returned from deployment to Iraq 7 months ago and celebrated with a trip to Las Vegas, NV. He presents to your office with complaints of low back pain, left knee pain, right ankle pain, heel pain, and red eyes. His symptoms began six weeks ago and have progressively gotten worse. He is experiencing prolonged morning stiffness in his low back, knee, and ankle lasting until midday and in the last week he has noticed swelling and warmth around his knee and ankle. He is no longer able to fully flex his knee and has difficulty ambulating. He has taken some over the counter Motrin with modest reduction in symptoms. He is otherwise healthy with no past medical history or allergies. On examination his left knee has a decreased passive range of motion and is warm to the touch. It is visibly swollen. His left ankle demonstrates
mild tenderness to palpation over the Achilles tendon and tenderness along the joint line. You perform an arthrocentesis of his left knee and remove 40ml of cloudy yellow synovial fluid. Microscopy reveals many wbc’s but no crystals. The cell count on the synovial fluid is 20,000 WBC’s per high power field. Additional laboratories obtained reveal a normal complete blood, count, complete metabolic panel, and a negative urine culture and gram stain. What additional finding would most strongly suggest reactive arthritis?

A) WBC 13,200 with normal differential (4,800-10,800/hpf)
B) Urethral swab with PMNs
C) Rheumatoid Factor 38 (0-24IU/ml)
D) ESR 42mm/hr(0-22mm/hr)

7) You decide to check an HLA B27 on this patient and are surprised when it comes back negative. Which of the following statements is true?

A) HLA B27 is positive in up to 80% of cases of classic reactive arthritis
B) The presence of HLA B27 is required to make a diagnosis of reactive arthritis
C) HLA B27 is occasionally negative early in the disease process and becomes positive in over 90%
D) HLA B27 is commonly seen in up 40% of the normal population

8) You are seeing a 10 year-old male with fever to 101 also has a swollen, hot, tender right knee. He fell off his skateboard 10 days ago and sustained an abrasion, but the pain acutely worsened in the past 24 hours. The most important initial step in management would be:

A) Obtain an x-ray to rule out a fracture
B) Perform a synovial fluid aspirate to evaluate for a septic joint.
C) Refer the patient to physical therapy for a knee sprain.
D) Strict limitation of physical activity until pain subsides.
Answers:
Answer (1): C. The classification of an arthritis helps define your differential diagnosis. In this case, the symptoms have been present for less than 6 weeks suggesting a broader differential which includes viral arthritis. Any arthritis affecting >4 joints is considered polyarticular.

Answer(2,3): A(2), C(3). This case represents a classic non-inflammatory polyarthritis. This is arthritis because the patient has lost range of motion in the affected joint. The pattern of articular involvement is most consistent with osteoarthritis or psoriatic arthritis, but the bulk of the evidence in this case suggests a non-inflammatory cause. The morning stiffness has a non-inflammatory pattern lasting only 15 minutes. There are no systemic inflammatory symptoms. Additionally, the symptoms get worse with activity and she exhibits the “gelling” phenomenon often seen with osteoarthritis. Finally, the radiographs are consistent with the classic findings of osteoarthritis (joint space loss, subchondral sclerosis, subchondral cysts, and osteophyte formation.) The erosions in this case are central, which can be seen in a specific form of osteoarthritis known as erosive OA. These erosions are typical central as opposed to the marginal erosions seen in erosive inflammatory arthritis such as rheumatoid arthritis. Given the distribution of arthritis in this case as well as the paucity of inflammatory signs or symptoms and the lack of evidence to suggest an underlying diagnosis of psoriasis, the likely diagnosis is OA.

Answer (4): C. Any monoarthritis is considered a septic arthritis until proven otherwise. The appropriate course of action is arthrocentesis with evaluation for cell count, culture, and crystal analysis. Laboratory evaluation, while helpful in this case, cannot be interpreted in the absence of synovial fluid analysis. Weight bearing radiographs of the knees may provide useful information, but does not help with determining the etiology of an acute inflammatory arthritis. Likewise, antibiotic administration would be inappropriate until a diagnosis of a septic arthritis is made.

Answer(5): D. Anti-Smith antibody is considered to be highly specific for a diagnosis of systemic lupus erythematosus with a specificity of nearly 97%. Likewise, dsDNA has a specificity of approximately 70%. The ANA has sensitivity of nearly 100% in the right clinical setting, such as this patient with a malar rash, arthritis, and fatigue, but is less specific. A low titer ANA, as in answer C, is very non-specific and can be seen in a variety of disorders and also in up to 10% of normal individuals. Rheumatoid factor can be seen in rheumatoid arthritis, but is very non-specific and can be seen in a variety of other conditions. CCP is very specific for rheumatoid arthritis (97%). ESR and CRP are very non-specific and can be elevated in a variety of infectious and inflammatory disorders.

Answer(6): B. A sterile pyuria would be an expected possible finding in a reactive arthritis. An elevated white count and elevated ESR, while associated with systemic inflammatory disease, is very non-specific. A slight elevation of rheumatoid factor can be seen in many conditions and is non-specific. Its presence or absence is not helpful in making a diagnosis of reactive arthritis.
Answer(7): A. Up to 20% of patients with a reactive arthritis will be HLA B27 negative. This makes it a poor diagnostic test, especially in cases which are unambiguous. This case clearly represents a case of classic reactive arthritis with evidence of low back pain, peripheral arthritis, enthesitis, and ocular involvement. HLA B27 testing is not needed as a negative result does not argue against the diagnosis. HLA B27 testing is most useful when the clinical picture is incomplete and the presence of HLA B27 can support the diagnosis. HLA B27 refers to the human leukocyte antigen region B27 of the major histocompatibility complex found on chromosome six. This is a genetic mutation and will not change over time. HLA B27 is present in 7% of the Caucasian population and less than 3% of the African American population.

Answer(8): B. This patient has a septic joint until proven otherwise. More conservative treatments could miss a severe bacterial infection requiring treatment. An x-ray is unlikely to reveal a fracture, given the fact that he did not have symptoms after his fall. A sprain also would have manifested symptoms earlier.
Intro to Clinical Reasoning: Monoarticular and Polyarticular Case Studies

Monoarticular Arthritis

Case #1

A 52-year-old retired Army E-6 is hospitalized for an angioplasty of his left anterior descending artery after suffering a “mild” heart attack. His risk factors for heart disease include hypertension, obesity, sedentary lifestyle, tobacco use and hypertriglyceridemia. The procedure goes well until the third day post-procedure when he complains acutely of a swollen red toe and ankle. It hurts so badly that he “cannot even stand the sheet touching it”. His medications before he was hospitalized included lisinopril and furosemide. After his heart attack, furosemide was stopped and aspirin and atenolol were added.

He states that he’s had similar pain in the past that has resolved over two or three days, but always in the other foot. He insists that the pain and erythema has never been this intense before. His past medical history is remarkable only for what has already been mentioned and acne rosacea. With the exception of some low-grade fevers (99.5 to 100.2), he feels well and is looking forward to leaving the hospital.

On physical examination, he is in moderate distress secondary to pain. His vital signs are normal and he is moderately overweight. His general examination is remarkable only for an S4 gallop. The groin site is clean with minimal tenderness on palpation and without drainage. His left big toe is diffusely swollen. It is hot, bright red, and extremely tender when bending the metatarsophalangeal joint. The medial aspect of his left ankle has a similar appearance with limited and painful range of motion.

Problem List:
1.
2.
3.
4.
5.
6.
7.
8.

Question #1
How would you characterize this man’s arthritis?

A. Acute, inflammatory
B. Acute, non-inflammatory
C. Chronic, inflammatory
D. Chronic, non-inflammatory

Question #2
Create a differential diagnosis of possible etiologies of this man’s arthritis. Be prepared to defend your choices, specifically mentioning evidence that supports or does not support your diagnoses.

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Question #3
What is the most important diagnosis to rule out in this patient?

Question #4
In creating your differential diagnosis, state the significance of the following features:

1. Age (52)

2. Gender (male)

3. Post-operative setting

4. Medications (past and present)

5. Past medical history

3:29
6. Low-grade fevers

**Question #5**
What is the most important diagnostic test?

You are impressed with the patient’s history and examination and elect to do the following: arthrocentesis, complete blood count (CBC), chemistry profile, uric acid, erythrocyte sedimentation rate (ESR), blood cultures.

The results are:

- **CBC**: WBC 8,600 with normal differential (nl 4,800-10,800); hemoglobin 13.6gm/dL (nl 14-18 gm/dL); platelet count 360,000 (nl 159,000-400,000)
- **ESR**: 32 mm/hr (nl <15 mm/hr)
- **Chemistry profile**: normal including BUN, creatinine, Ca, Phos, ALT, AST
- **Uric acid**: 5.6 mg/dL (nl <7 mg/dL)

The arthrocentesis was difficult and only a few drops were obtained, but the fluid was cloudy with poor viscosity.

**Question #6**
Of the following tests, which are the most important ones to be performed on the fluid? **Rank your choices from 1 to 5, with 1 being the most important.**

- A. Cell count
- B. Gram stain and culture
- C. Crystal analysis
- D. Protein
- E. Glucose

The gram stain on the fluid is negative and cultures are pending. The cell count on the fluid is 55,000 with 80% PMNs. Many PMNs have “spear-shaped” crystals within them that are yellow when aligned with the arrow of the polarized microscope.

**Question #7**
What is your diagnosis?

Question #8
Radiographs are performed on both feet. What clinical findings would you most likely see?

A. Periarticular osteopenia  D. Joint-space narrowing
B. Erosions with sclerotic margins  E. Normal plain films
C. Nodules in the soft tissue

Question #9
How would you manage this patient?
Polyarticular Arthritis:

Case #1

On Monday morning sick call, a 26-year-old Puerto Rican female SGT is seeing you for the first time. She has pain and swelling in her wrists, fingers, knees and feet for the past 6 months. Initially, she thought that she was “overdoing it” in her exercise class, but then became concerned when the pain and swelling persisted and involved more joints. Initially, the discomfort responded to aspirin, but now aspirin no longer seems to relieve her pain.

She has also noted intense fatigue and it takes at least 2 hours to “limber up” in the morning. She feels a little bit better by the time she gets to work, but has a terrible time doing PT with her unit. She denies fevers, chills, sweats, weight loss, rash or prior episodes of joint pain.

Her general physical examination including vital signs, heart, lungs, and abdominal examination are entirely normal. Her musculoskeletal examination is remarkable for mildly swollen, tender and erythematous wrists, 2nd and 3rd metacarpophalangeal joints as well as 2nd, 3rd, and 4th proximal interphalangeal joints bilaterally. Her right knee is slightly swollen and has a small effusion with decreased flexion. Her left knee is normal.

You are busy and recognize that she will require further testing, but you ponder the possible diagnoses in this patient.

Problem List:
1.
2.
3.
4.
5.
6.
7.
8.

Question #1
How would you characterize her arthritis?
A. Chronic, inflammatory symmetric arthritis
B. Acute, inflammatory symmetric arthritis
C. Chronic, non-inflammatory arthritis
D. Acute, non-inflammatory arthritis

**Question #2**
Create a differential diagnosis of possible etiologies of this service member’s arthritis. Be prepared to defend your choices, specifically mentioning evidence that supports or does not support your diagnoses.

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**Question #3**
In creating your differential diagnosis, state the significance of the following factors:

1. Age (26)
2. Gender (female)
3. Race (Puerto-Rican)
4. Pattern of joint involvement (small and large joints)
5. Amount of time to “limber up” (2 hours)

Even though you spent longer than what you would have liked to in thinking about her differential diagnosis, you also decide on your initial work-up. You order the following tests: complete blood count (CBC), rheumatoid factor (RF), anti-nuclear antibody (ANA), chemistry profile, Westergren erythrocyte sedimentation rate (ESR), and radiographs of her hands and wrists.
CBC:  WBC 6,500 with normal differential (nl 4,800-10,800); hemoglobin 11.2 gm/dL (nl 14-18gm/dL); platelet count 500,000 (nl 159,000-400,000)
ESR:  45 mm/hr (nl <15 mm/hr)
RF:  positive   **anti-CCP**  IgG:  97 units (normal 0-59)
ANA:  1:160 speckled pattern
Chemistry profile:  normal
Radiographs:  soft tissue swelling, juxta-articular osteopenia and small marginal erosions at 2nd and 3rd MCPs on both hands

**Question #4**
What is the significance of the following results and how does it change your differential diagnosis?

1. Hemoglobin of 11.2gm/dL
2. ESR of 45 mm/hr
3. Positive rheumatoid factor
4. Positive ANA
5. Anti-CCP IgG
6. Radiographic findings. What if the patient had normal x-rays?

**Question #5**
What is your final diagnosis?

**Question #6**
What would be your first steps in treating this patient?
Polyarticular Arthritis: Case Studies

Case #2

Later on in the morning, your last walk-in arrives. He is a 22-year-old second lieutenant complaining of a four-day history of pain in his wrist and knee.

He describes his health as being “excellent” and tells you he just “maxed” the April Army Personal Fitness Test (APFT). He is unmarried and lives by himself off-base. His symptoms started exactly 4 days ago when he awoke with pain and swelling in his left wrist. He could not work on his computer because it felt so bad. He didn’t think too much about it because it resolved over the next couple of days. However, at the same time he noted similar pain in his right wrist and left knee. Initially he denies other symptoms to include back pain, eye symptoms, diarrhea, chills and weight loss, but does note that he has had some low-grade fevers and perhaps a sore throat. (He does not have a thermometer so he cannot quantify them.)

He denies having had a sexually transmitted disease or a urethral discharge, but does admit that he is sexually active with “several” female partners as recently as two weeks ago.

On physical examination, he is a neatly dressed officer who appears mildly ill. His vital signs are unremarkable except for a temperature of 100.3. His general physical examination is normal except for two small pustules with surrounding erythema on the dorsal aspect of his left hand. (He hadn’t mentioned them to you, as he did not think them important.) His joint examination is remarkable for both his wrists being swollen, warm, and erythematous. In addition, there is significant discomfort when he tries to extend or flex his wrists with your resistance. The volar aspect is not swollen or tender. His right knee is also erythematous, warm, and painful to flex. He has no adenopathy, pharyngeal erythema or exudate.

Problem List:
1.
2.
3.
4.
5.
6.
7.
8.
**Question #1:**
How would you characterize his arthritis?

A. Chronic, inflammatory arthritis  
B. Acute, inflammatory arthritis  
C. Chronic, non-inflammatory arthritis  
D. Acute, non-inflammatory arthritis

**Question #2:**
What is the pattern of joint involvement?

A. Migratory  
B. Additive  
C. Palindromic

**Question #3:**
Which anatomical structures are likely to be involved (more than one may be correct)?

A. Forearm muscles (myositis)  
B. Tendon sheaths (tenosynovitis)  
C. Synovial lining of the wrist (synovitis)  
D. Skin in the region (cellulitis)  
E. Radioulnar bursa (bursitis)

**Question #4:**
Create a differential diagnosis of possible etiologies of this service member’s arthritis. Be prepared to defend your choices, specifically mentioning evidence that supports or does not support your diagnoses.

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3:36
Question #5:

In creating your differential diagnosis, state the significance (if any) of the following factors:

1. Pattern of joint involvement

2. Low grade fevers

3. Promiscuity

4. Sore throat

5. The “timing” of his arthritis

Your initial work-up includes the following: arthrocentesis with gram stain and cell count, chemistry profile, complete blood count (CBC), and erythrocyte sedimentation rate (ESR)

The results are:

CBC: WBC- 10,500 with a slight left shift (nl 4,800-10,800), hemoglobin- 14.2 gm/dl (nl 14-18 gm/dl), and platelet count 250,000 (nl 159,000-400,000)
ESR: 24 mm/hr (nl < 15 mm/hr)

Synovial fluid: culture- pending, WBC- 24,000 cells/mm³ (80% PMNs, 20% lymphocytes)

Gram stain-negative

Question #6: What additional laboratory or other testing would you do (more than one may be correct)?

A. Blister culture
B. Bilateral radiographs of hands and wrists
C. Urethral culture
D. Rectal culture
E. Rheumatoid factor (RF)
F. Radiographs of the sacroiliac joints
G. Throat culture
H. Streptococcal antigens
I. HIV
J. Antinuclear antibodies (ANA)
Question #7:
What is the significance (if any) of the following results?

1. White blood count and differential (10,500 cells/mm³)

2. Negative gram stain

3. Hemoglobin of 14.2 gm/dl

4. Negative synovial culture (results later reported as negative)

Question #8:
What is your final diagnosis?

Question #9:
How would you treat this patient?
Learning Objectives:
1. Define syncope and differentiate it from loss of consciousness due to seizure.
2. Describe the cerebrovascular events that result in syncope.
3. List the most common causes of cardiac and non-cardiac syncope.
4. Describe the sequence of events in neurally mediated syncope syndromes.
5. Describe the sequence of events in syncope due to cardiac electrical dysfunction.
6. Describe the sequence of events in syncope due to cardiac mechanical obstruction.
7. Describe the initial evaluation of a patient with syncope

Patient 1: A 22 year old Marine climbed a long hill on a hot, humid summer afternoon. Reaching the top, he removed his pack and squatted to arrange things inside. He stood up then fell to his knees and collapsed to the ground. Members of his unit shook him but he was unresponsive. He lay still with eyes rolled back for a minute or two as his comrades prepared to resuscitate. After they opened his airway, he emitted a strange shout and his limbs began to contract rhythmically. Then he gradually awoke, initially with some confusion but later seemed fully himself. A somewhat similar episode had occurred two years previously.

Questions: How would you characterize this episode? What physiological events might be responsible? What is the likely role of the heart in this situation? What features of the history and physical exam are relevant? What further diagnostic steps and treatments are in order?

What ifs: What if the patient described antecedent rapid heart beating (palpitations)? What if the patient had a persistently weak right leg after awakening? What if the patient’s younger brother had died suddenly?

Patient 2: An 85 year old man with a history of hypertension, benign prostatic hypertrophy, type 2 diabetes mellitus, and hyperlipidemia presented to the emergency department after experiencing sudden loss of consciousness. The event occurred approximately one hour after arising. The subject states that he had no symptoms prior to the event and felt weak but otherwise well immediately following. He denies chest pain, shortness of breath, or palpitations prior to the event. His wife witnessed the event, stating that it occurred without warning immediately after he stood up from a supine position, and that he regained consciousness almost immediately. Of note, he has no known active cardiac disease, and was seen two days ago by his urologist who prescribed a new medication to “help with his prostate.” But he neglected to bring his medications to the emergency department. In the emergency department, he is alert and oriented, and his supine physical examination is unremarkable with no evidence of a
murmur, gallop, jugular venous distension, adventitious respiratory sounds, or focal neurologic abnormality. On standing, his pulse rate went from 60 to 65 and his blood pressure from 135/70 to 110/70. His gait was normal and the Romberg test was negative. An electrocardiogram revealed normal sinus rhythm with normal intervals and no evidence of acute or past myocardial ischemia/infarction.

Questions: How would you characterize this episode?
What physiological events might be responsible?
What is the likely role of the heart in this situation?
What features of the history and physical exam are relevant?
What further diagnostic steps and treatments are in order?

What ifs: What if the patient had a loud systolic ejection murmur audible in his carotid arteries?
What if the patient had a persistently weak right leg after awakening?
What if the patient had a history of a myocardial infarction?

Methods:

A case format will be used. The case format will illustrate typical presentations or prototypes (basic illness scripts) and will also employ heuristics, and key feature approach. This section will largely use a pathophysiologic approach. The lecture time will be employed to review your understanding of the issues, as demonstrated by patient experience. So please prepare--
I. Syncope
Syncope is a sudden loss of consciousness and postural tone not due to epileptic seizures or trauma with spontaneous recovery. Syncope accounts for 6% of all hospital admissions. It is therefore a relatively common event. Syncope has a long differential diagnosis and can trigger a potentially endless series of tests. In some series, 50% of patients presenting with syncope never received a diagnosis. There is a significant degree of nihilism among house staff who bares the brunt of the diagnostic tour de force. More recent series have underscored the progress made in this area. The modern approach to syncope benefits from new techniques and new insights into the pathophysiology of this common problem, but ultimately depends on well-founded clinical reasoning.

II. Why do they lose consciousness? (Pathophysiology highlights)
Loss of consciousness (LOC) implies significant cerebral dysfunction. Loss of function must either occur in both cortical hemispheres or in the brainstem Ascending Reticular Activating System (ARAS). Therefore focal processes involving only one cortical hemisphere (like a middle cerebral artery stroke) should not cause complete LOC unless it triggers some other process, like a seizure. Unlike syncope, seizures result in a global depletion of neurotransmitters with a prolonged recovery phase. For this reason, generalized seizures cause prolonged confusion afterward. This is a fundamental historical point for differentiating seizures from syncope- immediately after syncope, the consciousness is clear.

Syncope is usually due to a brief interruption in blood flow to the brain followed by immediate restoration of flow. This allows restitution of brain energy stores before injury can occur. The vast majority of syncope is caused by a transient fall in cardiac output or loss of vascular tone. Thrombosis of a cerebral artery (stroke) takes minutes to hours to resolve. It is therefore rare for a stroke to cause transient loss of consciousness without persistent signs of neurologic injury. I emphasize this point because syncopal patients are frequently subjected to unnecessary neurologic evaluations.

III. Approach to the Syncopal Patient
When presented with a new clinical problem, consideration must be given to the "need to know" factor- in other words, how badly do you need to know the diagnosis? If the patient may be suffering from a potentially lethal condition, then the tempo of the evaluation must be intense until the potentially serious conditions are ruled out. A more relaxed, outpatient approach can then be taken.

Syncope fits this paradigm perfectly. Patients with syncope range from perfectly healthy to those at risk for immediate sudden cardiac death. Since it would be inappropriate to admit all these patients and subject them all to the same invasive tests, one must sort out who is at high risk and who is not.

Patients who have syncope due to cardiovascular disease have a one-year mortality of 20-30%, while patients with unknown or noncardiovascular syncope have a 5% one-year mortality. It is therefore critical to differentiate the patients who may have had cardiovascular syncope from those who did not.
Key finding in approaching the Syncopal Patient: Differentiating cardiovascular from non-cardiovascular syncope

Cardiovascular Syncope
The differential diagnosis for syncope is found in table 1. Cardiovascular syncope can be divided into problems of electrical instability and mechanical obstruction to blood flow. Syncope due to electrical instability is relatively common in elderly patients and patients with structural heart disease, and results in transient reductions in cardiac output.

Ventricular tachycardia should be suspected in anyone with syncope and a history of myocardial infarction, no matter how remote in time. The scar in the ventricle from the infarction acts as the reentry circuit for the tachycardia. Ventricular tachycardia can occur in otherwise healthy young people as well. An association of syncope during exercise or sudden stress can indicate a catecholamine-associated tachycardia or a pro-arrhythmic congenital abnormality such as the long QT syndrome or hypertrophic cardiomyopathy. Sudden sinus node arrest associated with Sick Sinus Syndrome or complete AV node block can result in syncope or cardiac arrest. A history of anginal chest pain preceding syncope may indicate the presence of acute myocardial ischemia triggering transient ventricular fibrillation. Mechanical obstruction can result in syncope due to either direct obstruction of blood flow through the central circulation, as in pulmonary embolus or atrial myxoma, or due to a resultant arrhythmia, as in aortic stenosis. Patients with syncope and chest pain may also suffer from aortic stenosis or hypertrophic cardiomyopathy and subvalvular stenosis. Finally, patients with long-standing hypertension may develop severe concentric left ventricular hypertrophy. Dehydration or the use of afterload-reducing drugs may result in acute under-filling of the ventricle, triggering a pump-priming failure and subsequent drop in cardiac output.

Table 1: Differential diagnosis of Syncope

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<td><strong>Cardiovascular Causes</strong></td>
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<td>Complete Heart Block</td>
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<td><strong>Mechanical Obstruction</strong></td>
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<td>Valvular or infravalvular</td>
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<td>Concentric Left Ventricular Hypertrophy</td>
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Noncardiovascular Syncope
The most common cause of syncope is neurally mediated syncope, accounting for 52% of cases in one series. This category contains a large number of apparently unrelated conditions which share a common mechanism—i.e., an interaction between brainstem reflexes and the heart and vascular system resulting in sudden reductions in either vascular tone, heart rate, or both. If the effect is primarily on vascular tone resulting in vasodilatation and loss of blood pressure, then it is called a “vasodepressor” response. If the effect is to cause bradycardia, then it is termed a “cardioinhibitory” response. Frequently both effects are present.

The common faint, occurring in the setting of pain or emotional stress such as blood donation or standing at attention, is a type of neurally mediated syncope often referred to as a “vasovagal” episode (figure 1). Such episodes occur in otherwise healthy individuals, and typically have prodromal symptoms of nausea, weakness, flushing, lightheadedness, and pallor. The patients often continue to experience weakness and fatigue for hours or even days afterwards. While cortical input may be enough to trigger such an event (i.e., the sight of blood), dehydration or venous pooling in the extremities greatly enhances the likelihood of syncope. It is thought that a reduction in venous return to the heart results in the stimulation of mechanoreceptors that stimulate C-fiber afferents. These in turn stimulate the nucleus tractus solitarius, triggering a counterproductive reflex. Rather than causing parasympathetic withdrawal and an increase in sympathetic tone to elevate the heart rate and vascular tone, the opposite effects are seen. Sympathetic tone drops, resulting in vasodilatation and hypotension. Simultaneously an increase in vagal tone occurs with significant bradycardia which may either be relative (i.e., too slow for the given blood pressure) or absolute, with prolonged periods of asystole or complete heart block common even in normal hosts (see Figure). Placing patients on a Tilt Table at 60° can reproduce this sequence. If it reproduces the patient’s symptoms, it is regarded as diagnostic. This sequence of events also underlies micturition syncope, a common condition in older men who lose consciousness after straining to void (Valsalva maneuver), usually after a night’s sleep. It is thought that the Valsalva strain reduces
Venous return acutely. Finally, carotid sinus hypersensitivity is a relatively common form of neurally mediated syncope in the elderly. Stimulation of the carotid sinus (usually the right side) results in both vasodepression and cardioinhibition and is classically described in elderly men while shaving.
Other noncardiovascular causes of syncope include the rare temporal lobe seizure which can result in syncope without causing post-ictal confusion. Finally, patients with frequent, non-injuring syncope who have otherwise negative evaluations may suffer from conversion syncope, a psychiatric condition more prevalent in the young active duty population.

IV. Evaluation of the Syncopal Patient- History

A careful history renders the proper diagnosis in 50% of syncope patients. A careful description of the setting, premonitory symptoms, presence of post-syncopal confusion, incontinence, neurologic dysfunction should be elicited. Comparison with a bystander history is often very illuminating. Certain specific historical points should be considered:

- Emotional stress, pain, crowded room, an urge to defecate, prolonged sun exposure, nausea, pallor, diaphoresis, and post-syncopal fatigue- may indicate a vasovagal episode or other neurally mediated event. Brief seizure-like motor activity is not unusual in syncope, but if significant post-ictal confusion is present, then a seizure probably occurred.

- The presence of a family history of sudden death should be rigorously sought. Unexplained death or a history of syncope in a sibling may indicate an inherited disorder such as the Long QT syndrome (LQTS; an ion channel disorder resulting in ventricular tachycardia) or Hypertrophic Cardiomyopathy (HCM). Both are autosomal dominant.

- Syncope after exercise may be due to a vasovagal episode, but syncope during exercise is very worrisome, and may indicate a significant propensity for sudden death such as HCM or LQTS.

- Multiple episodes of syncope demand immediate evaluation.

A careful past medical history for evidence of cardiac disease is essential. A history of chest pain, infarction, heart failure, valvular disease, or multiple cardiac risk factors identifies a patient at high risk. A history of palpitations prior to syncope may indicate the presence of a tachyarrhythmia, although patients with ventricular tachycardia frequently have no premonitory symptoms.

The absence of premonitory symptoms is worrisome for arrhythmia and should be evaluated closely. Similarly, patients who are injured during syncope are more likely to have had a cardiovascular cause of syncope, although elderly can be injured during syncope of any kind.

Syncope in individuals with high risk occupations- i.e. pilots, school bus drivers- need expedited evaluation.
A careful medication and drug use history is essential. Blood pressure medications are particularly prone to causing orthostatic hypotension that is a common noncardiac cause of syncope in the elderly.

**Diagnostic Evaluation for Syncope**

- Careful medical history, bystander reports
- Physical Exam
- EKG
- Chest X-ray
- Echocardiogram

**Evidence of Structural Heart Disease?**
- High Suspicion for Arrhythmia?
- High-Risk Patient?

**Suspect Vasovagal episode in young, healthy patient?**
- **NEG**
  - Tilt-table Testing
  - Carotid Sinus Massage
  - **NEG**
  - Directed Therapy based on Specific Diagnosis

**Admit to Hospital for Monitoring**

**CONSIDER**
- **EP Study**
- Coronary Angiography
- Exercise Testing

**Long Term EKG**
- Tilt-Table Testing
- ?Neurologic Consult
- ?Psychiatric Consult
V. Evaluation of the Syncopal Patient- Physical Exam
Particular attention should be given to the vital signs. Blood pressure and pulse should be measured supine and standing. A drop in systolic pressure greater than 20 mmHg, diastolic pressure greater than 10 mmHg, or an increase in pulse rate greater than 10 bpm suggests significant volume depletion or autonomic dysfunction due to disease (i.e. diabetes, Parkinson’s Disease are common causes). A fall in diastolic blood pressure may indicate poor autonomic function.

Evidence of structural heart disease such as gallop sounds, heart murmurs (particularly the crescendo-decrescendo murmur of aortic stenosis), delayed carotid upstrokes, and pulmonary rales should be diligently sought.

A careful neurologic exam should be done. Any residual neurologic deficit suggests that the patient had a stroke or seizure and is not consistent with syncope.

VI. Evaluation of the Syncopal Patient- Ancillary tests
The EKG should be examined for signs of acute ischemia, heart block, old myocardial infarction, ventricular pre-excitation, prolonged QT interval, and ventricular hypertrophy.

Obtaining routine blood chemistry is rarely useful. Hypoglycemia is associated with altered mental status, falls, or generalized seizures, but rarely with true syncope.

In the young patient with a single vasovagal episode occurring in the right setting, no further evaluation is probably required. All others should have echocardiography in order to rule out structural heart disease.

Elderly patients, patients with presumed structural heart disease, those with a probable arrhythmia, and those otherwise thought to be at high risk, should be admitted to a ward with continuous EKG monitoring (cardiac telemetry). Further invasive studies may be appropriate, particularly for those with previous myocardial infarctions who are at high risk for lethal arrhythmias.

Patients without structural heart disease and those with negative invasive evaluations can usually be evaluated as outpatients with Tilt testing or long-term ambulatory EKG monitors. These modalities have significantly increased the diagnostic yield, giving a diagnosis in as many as 60% of previously undiagnosed patients.

Finally, those patients with multiple syncopal episodes and negative evaluations should be considered for neurologic and/or psychologic evaluation.
Returning to our patient…
Returning to our syncopal Marine, we can now approach the questions posed at the beginning of the chapter. Remember, in clinical reasoning, we rarely reach a “correct answer” at the initial evaluation. It is critical to frame the questions for future evaluation correctly and to consider the “what if” facts which will radically alter our evaluation.

Questions for Patient 1:
How would you characterize this episode?
This appears to be a syncopal episode, i.e. there is transient loss of consciousness not attributable to a seizure (see below) or trauma. The duration of the confusion is important to establish with witnesses, but if less than 10 minutes, it is unlikely that a grand mal seizure has occurred.

What physiological events might be responsible?
The setting is very important. Note that he lost consciousness when rising from a squatting position after exertion that likely resulted in dehydration. Both would represent a challenge to his homeostatic mechanisms and put him at risk for a neurally mediated syncopal event.

What is the likely role of the heart in this situation?
If the hypothesis is correct, i.e. that this is a neurally mediated syncope, then the heart is an innocent “bystander.” If, however, certain facts were changed we would be less confident. If he reported chest pain or lost consciousness while walking we would be more concerned that this was a cardiovascular syncope due to obstruction or arrhythmia. The presence of “palpitations” prior to the event would also be concerning for an arrhythmia. The presence of a family history of sudden death greatly increases concern that the event was not benign as well.

What features of the history and physical exam are relevant?
A description of the subject’s symptoms (if any) prior to and following the event are extremely useful for differentiating benign neurally mediated syncope from potentially life-threatening cardiovascular syncope. The presence of nausea or progressive loss of vision for more than 5 seconds prior to the event and fatigue, nausea, or the desire to void afterwards are all suggestive of autonomic activation. The absence of these features favors cardiovascular syncope and merits a much more aggressive evaluation.

What further diagnostic steps and treatments are in order?
Measurement of orthostatic blood pressure and pulse as well as a cardiovascular physical exam may be all that is appropriate unless cardiovascular syncope is suspected. The presence of orthostasis would merit re-hydration, but the absence of orthostasis does not rule out neurally mediated syncope.

What ifs:
What if the patient described antecedent rapid heart beating (palpitations)?
As discussed above, these symptoms do increase the likelihood that an arrhythmia.

What if the patient had a persistently weak right leg after awakening?
While this is a very unusual finding, it is not consistent with a syncopal event. Unless trauma resulted in a peripheral nerve injury, one would be very concerned of a central nervous system injury.

*What if the patient’s younger brother had died suddenly?*
See above. This fact greatly increases concern for a potentially life threatening cause of syncope or sudden cardiac death.

**Questions for Patient 2:**

*How would you characterize this episode?*
This appears to be a syncopal episode, i.e. there is transient loss of consciousness not attributable to a seizure (see below) or trauma. The presence of a witness is very helpful in establishing the time course of events, and one should insist on speaking to witnesses whenever possible rather than relying on the opinions of the patient or EMTs.

*What physiological events might be responsible?*
It is probably significant that the event occurred shortly after standing. The absence of premonitory or post-dromal symptoms is fairly common in the elderly who may have no warning before their event regardless of the cause.

*What is the likely role of the heart in this situation?*
Heart disease is highly prevalent in the elderly, and the fact that the subject does not believe that he has any cardiovascular issues is not particularly helpful. In the absence of a convincing alternative diagnosis, it is frequently best to admit elderly patients with syncope for a more extensive evaluation, i.e. overnight telemetry, an echocardiogram, and other tests as needed. In this case, the scenario points towards orthostatic hypotension induced by a newly prescribed medication. Orthostatic hypotension is most commonly seen in diabetics, hypertensive individuals on medications, and Parkinson’s Disease. Medications that interfere with homeostatic mechanisms, particularly diuretics and blockers of the $\alpha$- and $\beta$-adrenergic receptors are most likely to exacerbate any tendency towards orthostatic hypotension.

*What features of the history and physical exam are relevant?*
The history points to a newly prescribed medication that could be expected to induce postural hypotension. The presence of a $>20$ mm Hg drop in the systolic blood pressure or $>10$ mmHg drop in diastolic blood pressure after standing for 3 minutes confirms the presence of orthostatic hypotension. In this instance, a medication interaction is the likely cause, but one needs to consider occult bleeding or other cause of intravascular volume depletion. Taking vitals in the supine and standing positions is a critical part of the evaluation of ANY subject with syncope, and is probably the single most useful physical exam maneuver in syncopal subjects. It is also possible to have positive orthostatic measurements with an alternative diagnosis responsible for the syncopal event.

*What further diagnostic steps and treatments are in order?*
Assessment of the blood counts and possibly a rectal examination looking for occult blood would be indicated to help rule out gastrointestinal blood loss. Given the subject’s age,
admission to the hospital (to a specialized unit with electrocardiographic monitoring) for further observation (looking for arrhythmias such as transient atrioventricular block) is still reasonable.

**What ifs:**

*What if the patient had a loud systolic ejection murmur audible in his carotid arteries?*
This physical exam finding would indicate some degree of turbulent flow in the aortic outflow tract and would be consistent with valvular aortic stenosis (among other possibilities). Valvular aortic stenosis is most common in the elderly and, when associated with syncope, may indicate a very high risk for sudden cardiac death. Such a patient should undergo a careful examination of his carotid pulsation. The presence of a late, low volume pulse could indicate critical aortic stenosis, a highly lethal condition in the absence of valve replacement surgery.

*What if the patient had a persistently weak right leg after awakening?*
If this were a new finding, it might indicate a cerebrovascular accident, which is an extremely rare cause of syncope. In the absence of a focal neurologic finding such as unilateral leg weakness, performing further neurologic testing (such as brain imaging or carotid ultrasounds) is a waste of time and money.

*What if the patient had a history of myocardial infarction?*
The presence of a history of cardiovascular disease increases the likelihood that this event was in fact cardiogenic in origin. In such an individual, the presence of orthostatic hypotension may well prove to be a “red herring” that should not distract the clinician from admitting the subject to the hospital for a more extensive cardiac evaluation in order to prevent possible sudden cardiac death.
Your last patient of the day is a 16 year old girl with a chief complaint of ‘passing out.’ You correctly recall that syncope is a common condition in children, especially in adolescent females. You thumb through the chart and notice this young girl has no significant past medical history, is not followed for any ongoing conditions and is taking no medicine. You enter the room to find a happy, cheerful, athletic young girl with whom you easily establish rapport. You find out that she had been in her usual state of good health until this afternoon when she ‘passed out’ during the middle of soccer practice. The coaches tell her she was ‘out’ for less than a minute. She doesn’t recall feeling dizzy or lightheaded prior to the event, and she denies any recent illness. They made her sit out the rest of practice until her parents could bring her into your clinic. She seems to be most upset about missing the scrimmage.

Her physical exam reveals a healthy, athletic young girl in no distress. Her vital signs are all normal and there are no abnormal findings on exam.

The pathophysiology of syncope in children is no different than in adults and results from the brief interruption in blood flow to the brain. Likewise, as in adults, it can be classified into cardiovascular and non-cardiovascular syncope. However, unlike adults, cardiovascular syncope is exceedingly rare. A detailed history and physical exam is the key to separating out the benign from the potentially life threatening causes of syncope.

A thorough history and physical exam are the most important task in the approach to a child with syncope. As seizures are not a rare occurrence in children (up to 10% of children will experience at least one, most commonly simple febrile seizures), it is first essential to determine whether this was a true syncopal event or an event that mimics syncope. Past medical history (similar past events, history of febrile seizures), family history (epilepsy or other seizure disorder), post-ictal confusion, loss of bowel or bladder control (obviously difficult to assess in incontinent infants and toddlers), and repetitive tonic-clonic movements could all suggest seizures. Once you are convinced the episode is syncope, the next step is to determine the etiology.

Cardiovascular cause for syncope in children is incredibly rare but can be fatal if missed. Again, a careful history and physical exam can help you differentiate. The most common cardiac causes of syncope (and sudden death) in children are long QT syndrome and hypertrophic cardiomyopathy. Detailed past medical history (i.e. congenital heart disease), and family history are very important, with particular attention to sudden deaths in the family. **If the syncope occurs during exercise then it is cardiovascular syncope until proven otherwise.** Asking about sudden death in family members, including drowning, is essential. Post exercise syncope may be neurally mediated, but syncope during exercise demands additional investigation. Other causes for cardiovascular syncope include anything that results in severe left ventricular outflow obstruction (aortic stenosis) or cardiac arrhythmias (supraventricular tachycardia including Wolff Parkinson White syndrome, complete AV block, or sinus node dysfunction). Older children will describe their hearts as ‘racing’ when SVT is present, but younger children and infants may have very nonspecific signs including being fussy or refusing to eat.
Far and away the most common cause of syncope in children is a vasovagal episode. Less common in children under 10, this condition is very common among adolescents, especially females. The pathophysiology is the same as described in adults. The classic case is the junior high school girl in biology class attempting to dissect frogs. Prolonged standing (leading to subsequent venous pooling), warm environment, pain and fear can all precipitate vasovagal syncope. The patient generally experiences nausea, weakness, flushing, lightheadedness, and often describes a gradual ‘graying’ out before complete loss of consciousness. With this classic story and a normal physical exam, nothing is needed but reassurance (and in fact, most patients and parents don’t seek medical care for such an event). For recurrent episodes, the previously mentioned Tilt Table test can help solidify the diagnosis.

Finally, a few words on a diagnosis of syncope unique to children—Breath Holding Spells. While harmless, these episodes are very frightening to parents because the child becomes lifeless and unresponsive secondary to cerebral anoxia at the height of the attack. There are two forms—the more common cyanotic form and the less common pallid type. These events are uncommon before age 6 mo., peak at age 2, and usually resolve by 5 yrs. They start with a provocation (usually scolding or upsetting the child) to which the child responds with a brief, shrill cry followed by forced expiration and apnea. Cyanosis and loss of consciousness then rapidly develop, occasionally accompanied by generalized clonic jerks. With this classic story, further investigation is unwarranted.

As you leave the room and prepare to present this patient to your preceptor, something doesn’t sit quite right. You were expecting her to have the typical teenage girl vasovagal syncope, but she didn’t endorse any of the usual symptoms (i.e. feeling flushed, nauseous, ‘graying out’) and what really worries you is the fact that this syncopal episode occurred during exercise. You re-enter the room and ask a few more questions and learn that an uncle had died at a very young age of a bizarre drowning accident. This furthers your concern for possible cardiac etiology. Though her exam is normal, you decide to suggest to your preceptor that you believe additional investigative studies are warranted. You suggest an EKG to look for evidence of prolonged QT and hypertrophic cardiomyopathy (left ventricular hypertrophy on EKG) and ultimately would like to consult with a pediatric cardiologist for definitive evaluation.

VII. Conclusions
The evaluation of syncopal patients should emphasize the identification of possible cardiovascular causes. A careful history and physical is a powerful diagnostic tool if correctly performed. In many patients, no further evaluation is necessary, but in a significant number, further noninvasive and invasive testing is necessary.
Practice questions (and answers)
1. A 62 year old male presents to the Emergency Department following a syncopal episode. If you were considering a diagnosis of vasovagal syncope and you learned that the patient passed out while standing in line at the pharmacy, this diagnosis becomes:
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely

2. A 62 year old male presents to the Emergency Department following a syncopal episode. If you were considering a diagnosis of ventricular tachycardia and you learned that he has a history of coronary artery disease, this diagnosis becomes:
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely

3. A 24 year old female presents to the Emergency Department following a syncopal episode. If you were considering a diagnosis of vasovagal syncope and you found that she has multiple facial contusions on examination, this diagnosis becomes:
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely

4. A 74-year-old retired Army General comes to the clinic with decreasing exercise tolerance of 6 months' duration, new onset lower extremity edema, as well as feeling like he is going to pass out with exertion. He has dyspnea with chest pain when he walks briskly or up stairs. He has had two episodes of syncope with exertion over the past month. He underwent single-vessel percutaneous transluminal coronary angioplasty 4 years ago. Medications include aspirin, 81 mg/d, and atorvastatin, 20 mg/d. On physical examination, his heart rate is 82/min and blood pressure is 142/84 mm Hg. A harsh 4/6 crescendo-decrescendo systolic murmur is noted at the right upper sternal border and radiates to the carotids. The murmur diminishes with the Valsalva maneuver. Additionally, his carotid upstroke is diminished in intensity and his S2 is soft. Which of the following is the MOST LIKELY cause of his presentation?
   a) Aortic dissection
   b) Aortic stenosis
   c) Pericarditis
   d) Panic Attack
Mitral Regurgitation

5. You are sitting in lecture hall where a dermatologist is showing slides of various rashes. Your friend and classmate who has been standing during the lecture (he was out late last night), passes out and then abruptly jerks his hands and feet for a period of seconds. He does not appear to have a physical injury, did not bite his tongue, and did not have bowel or bladder incontinence. He appears a bit pale and embarrassment, but is coherent and reports that he just felt the onset of nausea while his vision gradually faded to a pinpoint before going black. He reports no recent illness, no significant past medical history, and takes no medications. You escort him to the Student Health Clinic, where the physician documents normal vital signs and a 1/6 systolic ejection murmur at the left upper sternal border that does not increase with inspiration or Valsalva. Electrocardiogram is normal. What is the MOST LIKELY diagnosis?

a) Vasovagal syncope    
b) Aortic stenosis     
c) HOCM (hypertrophic obstructive cardiomyopathy)  
d) Ventricular tachycardia  
e) Alcohol withdrawal seizure
Answers:
1. A (much more likely). Standing in line for a long period of time can predispose to venous pooling and thus vasovagal syncope.
2. A (much more likely). Coronary artery disease is the leading risk factor for ventricular tachycardia. Gathering this information would make the diagnosis much more likely.
3. B (much less likely). Patients with vasovagal syncope usually do not sustain major injury following their syncopal spell. This is something much more consistent with cardiovascular causes of syncope.
4. Classic description of AS murmur and AS is a cause of presyncope as well as syncope.
5. This is a quite classic case of vasovagal syncope. The murmur is not consistent with AS (this would be very unusual in this patient's age) or HOCM. Ventricular tachycardia should be strongly considered in patients with a h/o CAD who experience syncope or in folks who have syncope with exertion. Though he may have had some alcohol, this is not a seizure--would expect additional findings to include post-ictal confusion which this patient did not have or other findings often associated with seizure (i.e., tongue biting or bowel/bladder incontinence).
ICR small group case discussions will immediately follow the ICS Oral Case Presentations and Feedback for each preceptor small group.

In ICR small group sessions, your preceptor will facilitate a discussion of key clinical aspects in each case. The goals of each and every ICR small group are to develop clinical reasoning skills as the fundamental building blocks of clinical medicine. These goals are achieved via the following objectives independent of the content specific objectives:

1) Illustrate major diagnostic entities (common and/or serious) for the topic.
2) Describe typical patterns of presentation for these diagnostic entities (classic or typical patterns)
3) Construct a prioritized problem list for each case
4) Create a relevant differential diagnosis for each case
5) Demonstrate clinical reasoning by justifying the differential diagnosis using key clinical information or decision points towards establishing the diagnosis
6) Reinforce use of proper medical terminology and pathophysiology germane to each case

Every ICR small group is intended to be a “low-stakes” learning environment where active participation is encouraged and supported with content and context-specific preceptor feedback. Preceptors will assess your clinical reasoning through active listening as you discuss problem lists, differentials, and management aspects for each case. Preceptors will use a number of techniques to encourage participation so they can observe and assess your clinical reasoning skills. Preceptors also model clinical reasoning in their approach to each case.

*It is worth mentioning again -- Without active participation, preceptors will not be able to assess your understanding of the cases or focus the discussion on necessary aspects of clinical reasoning to improve your clinical reasoning skills. For this reason, active participation is required!
ICR Syncope Cases
The small group cases for this session will be the 3 patients that you will discuss as part of your Integrated Clinical Skills (ICS) experience on this topic.

Please complete the form on the next page for the patient that you wrote up during your ICS session. This form must be turned into your ICR preceptor at the beginning of the ICR small group session on this topic to receive credit. If you do not complete the below in advance, it will impact your ICR small group grade for the session.

Please be prepared to give a 3 to 5 minute presentation of this patient for your ICR session. Your ICR preceptor will ask for someone to present each of the three cases.

For each of the cases, you should ask yourself the following critical questions:
1. Did the patient experience syncope? Why or why not? What does the patient's major motor activity during the episode tell you, if anything?

2. Does the nature of the patient's episode help you differentiate between cardiovascular and non-cardiovascular etiologies? What is the significance of syncope occurring during exercise?

3. What importance do you attach to the patient's past medical and family history?

4. How useful is the physical exam in the differential diagnosis of syncope?
**Prioritized problem list**
1.
2.
3.
4.
5.
6.

**Prioritized differential diagnosis** (include at least 3 diagnostic options)
1.
2.
3.
4.
5.

**Justification for leading diagnosis** (history and physical exam findings and any ancillary data provided; write as a paragraph):

**Plan** (diagnostic work-up and/or therapeutic)
1.
2.
3.
4.
Syncope- Case Studies

Case 1
An eighteen year-old white female Army recruit was in her usual state of excellent health when she experienced transient loss of consciousness during her two mile run.

The patient reported feeling well on the day of her test except for the onset of typical lower back pains that she associated with her menstrual cramping. She had not noted any vaginal bleeding, but expected it to begin either that day or the next. She ate a typical breakfast of dry cereal with milk and orange juice before reporting for her semiannual PRT.

She accomplished her push-ups and sit-ups without difficulty. She agreed to compete with a friend during the two-mile run to see who could enter the better time. Although she has no memory of the run, her friend reported that she was doing well and running faster than she had previously when she abruptly stumbled and hit the ground. Other runners stopped to provide assistance, noting that she made no effort to break her fall and consequently sustained several facial lacerations from the impact. On the ground she was unresponsive, and after about ten seconds manifested tonic-clonic movements in her legs and arms. By the time a corpsman arrived, however, she regained consciousness and recognized her surroundings and her friends.

The corpsman found her to have a pulse of 110 and a blood pressure of 125/65 mm Hg. She was alert and oriented, but had no memory of falling. In the emergency room, her pulse was 72, and her blood pressure 100/70 in both arms. With standing her pulse was 78 and blood pressure 100/75, respirations were 12, and she was afebrile. Her physical exam was remarkable for the presence of a brief early systolic murmur in the pulmonic area that did not radiate and a soft third heart sound at the apex. Valsalva made the murmur less intense.

On questioning, the patient admitted to having had multiple previous episodes of near-syncope or complete loss of consciousness that she had suppressed during her original induction interview. These episode typically occurred with severe emotional stress. She had been told by her family doctor that she would "grow out of them." She was on no medications and denied any illicit drug use.

Family history was significant for a brother who drowned during a 1-mile swimming race across a lake. She had been told that he had a "seizure disorder," and she had seen him once lose consciousness during a fistfight.

Bloodwork was significant only for a glucose of 65. Her EKG showed normal sinus rhythm at 72 with a P-R interval of 160 ms, no ventricular pre-excitation, and a rate corrected QT interval of 500 ms with flattened T-waves in lead II.
Questions-
1. Did the patient experience syncope? Why or why not? What does the patient's major motor activity during the episode tell you, if anything?
2. Does the nature of the patient's episode help you differentiate between cardiovascular and non-cardiovascular etiologies? What is the significance of syncope occurring during exercise?
3. What importance do you attach to the patient's past medical and family history?
4. Is the physical exam helpful here?Chemistrys? Electrocardiogram?
5. What is the most probable explanation for the patient's episode? Does the patient's menstrual history help your differential diagnosis? What is the relation between exercise and her episode?
6. Discuss how you would evaluate this patient further. Does she need admission to the hospital? Any further tests? Are a head CAT scan or electroencephalogram appropriate?

Case 2
An eighteen year-old white female Army recruit was in her usual state of excellent health when she experienced transient loss of consciousness following her two-mile run.

The patient reported feeling well on the day of her test except for the onset of typical lower back pains that she associated with her menstrual cramping. She had not noted any vaginal bleeding, but expected it to begin either that day or the next. She ate a typical breakfast of dry cereal with milk and orange juice before reporting for her semiannual fitness test.

She accomplished her push-ups and sit-ups without difficulty. She agreed to compete with a friend during the two-mile run to see who could enter the better time. During the run she felt very hot and was sweating profusely. She barely completed the run, and immediately felt nauseated. She remembers wanting to sit down under a tree, but her friend approached her and questioned her about her poor performance. Her friend commented to her that she looked pale. The patient recalled that she was having difficulty concentrating, and that her friend's voice seemed unusually loud and grating. At this point she fell forward, losing consciousness. Witnesses recalled that she seemed to be lowering herself to the grass. She regained consciousness after 10-20 seconds on the ground, but still looked quite ashen and diaphoretic for several minutes. A corpsman noted a thready pulse with a rate of 40 bpm, and her blood pressure was 70 systolic by palpation.

In the emergency room the patient reported feeling fatigued and anorexic, but she was completely oriented to her surroundings. On physical exam her pulse was 72, and her blood pressure 100/70 in both arms. With standing her pulse was 78 and blood pressure 100/75, respirations were 12, and she was afebrile. Her physical exam was remarkable for the presence of a brief early systolic murmur in the pulmonic area that did not radiate and a soft third heart sound at the apex. Valsalva made the murmur less intense.
On questioning, the patient admitted to having lost consciousness while standing in Church during a particularly long service and once while giving a blood donation. She also recalls feeling hot and nauseated before these episodes. She exercises five times a week, but usually indoors on a "Stair-Stepper" or treadmill. She denies ever having syncope or pre-syncope during exercise. She has two brothers and two sisters, all in good health. Her grandmother died suddenly at age 75.

Bloodwork was significant only for a glucose of 65. Her EKG showed normal sinus rhythm at 72 with a P-R interval of 160 ms, no ventricular pre-excitation, and a rate corrected QT interval of 420 ms in lead II.

Questions-
7. Did the patient experience syncope? Why or why not?
8. Does the nature of the patient's episode help you differentiate between cardiovascular and non-cardiovascular etiologies? What is the significance of syncope occurring following exercise?
9. What importance do you attach to the patient's past medical and family history?
10. Is the physical exam helpful here? Chemistry? Electrocardiogram?
11. What is the most probable explanation for the patient's episode? Do the patient's premonitory symptoms help make the diagnosis? What is the relation between exercise and her episode? How do you explain the patient's vital signs immediately after the episode?
12. Discuss how you would evaluate this patient further. Does she need admission to the hospital? Any further tests? Are a head CAT scan or electroencephalogram appropriate?
13. How would your evaluation be affected if the patient was seventy years old instead of eighteen?
A 35 year old. Air Force pilot fell from his motorcycle, bruising his anterior chest. He was dazed and a little short of breath after the incident occurred but only complained of superficial chest soreness. Six hours later, he had marked worsening of chest pain and shortness of breath, particularly with effort.

QUESTIONS:
1) What are the possible causes of the patient’s symptoms?
2) How would these causes affect the patient’s current and future function?
3) What features of the patient’s history are of particular importance?
4) How would the physical exam help identify causes and consequences?
5) What further diagnostic steps and treatments are in order?
6) What if the patient became dizzy and noted erratic heart action?
7) What if the patient noted bulging neck veins?
8) What if the patient developed a new heart murmur?

LEARNING OBJECTIVES: By the end of this session the student should:
1. Understand the pathophysiology responsible for the development and relief of angina pectoris
2. Describe classic chest pain syndromes: history and physical exam presentations for: MI/acute coronary syndrome, pericarditis, pulmonary embolism, aortic dissection, chest wall pain
3. Understand the triage of patients with chest pain—identify low-risk vs. high-risk patients based on presenting symptoms, medical history, physical findings, electrocardiogram, and lab results
4. Understand the pathophysiology of stable and unstable (or acute) coronary syndromes. How can you differentiate these syndromes by history and physical exam?

METHODS:
A case format will be used. The lecture time will be employed to review your understanding of the issues, as demonstrated by patient experience. So please prepare. This section will employ a pathophysiological approach to the diagnosis of chest pain with emphasis on coronary syndromes. Reasoning tools with this approach are key features of the presentation, pattern recognition (basic illness scripts) and heuristics.

READ the case material before the lecture.

ANSWER the case questions.

LOOK UP information as needed.
CHEST PAIN: CASES FOR LECTURE DISCUSSION
ENCOUNTER #1

Captain Green is a 52 year old male evaluated because of newly-developed, recurrent substernal chest discomfort. He has previously been in good health while pursuing an active lifestyle. During the past four weeks, strenuous activity--such as running--has gradually brought on a dull squeezing sensation deep in his chest, behind the breast bone. If he persists in the strenuous activity, this sensation steadily worsens, and he also develops a poorly-localized ache in his left arm. When he stops, discomfort eases and then resolves completely over about 1-2 min.

What features of CAPT Green's symptom make you think that this is angina pectoris? Consider the qualities of his symptom by applying categories you would use for any painful symptom:

- **Onset**: Describe how and when the symptom first appears?
- **Palliation/Provocation**: What precipitates the symptom and what makes it better or worse? How does the patient’s discomfort change with exercise? How does it change with rest?
- **Quality**: Characterize the pain/symptom (i.e. stabbing, dull, pressing, aching, etc.)
- **Radiation**: Does the pain travel within or outside the chest? (i.e. into the neck, jaw, arm, back etc.)
- **Severity**: Describe the intensity of the pain/symptom on a scale of 0-10
- **Temporal**: When does the pain/symptom occur? How long does it last? How frequently does it occur? What circumstances hasten the appearance of pain (e.g., cold exposure, meals, upset)?

What structures other than heart muscle, might be a source of chest pain in this patient? Consider: pleura and bronchi, pericardium, aorta, esophagus and stomach, chest wall muscle, and bone. Patients experiencing panic attacks, a psychiatric symptom, often present with chest pain. What clinical features typify pain from each of these different alternative sources?

Why is anginal discomfort associated with effort? Why is it alleviated by rest? Think in terms of myocardial ischemia: what circumstances bring on ischemia? Which of these circumstances will occur regularly with exercise and reverse with rest? How can these be quantitated?

What is the most likely anatomic abnormality responsible for angina pectoris in this patient? What if CAPT Green had a loud systolic ejection murmur in the aortic area--how would this change your thinking? What is this patient's long-term outlook if he has coronary disease? What if he has aortic valve disease?

CAPT Green noted unusual shortness of breath coming on just before chest pain. How could this be related to the same pathophysiology leading to angina pectoris?
CHEST PAIN: ENCOUNTER #2

CAPT Green has now been treated with appropriate drugs for two years. His exertional symptoms have remained stable (and rare) until three nights ago. He was then awakened by the same discomfort he had experienced previously only during exercise. The symptom gradually receded when he sat up in bed and put a nitroglycerin tablet under his tongue. It reappeared during the ensuing days when climbing a single flight of stairs or walking a few hundred yards, particularly when he performed activity just after meals or in a chilly environment. Previously, the same effort had not caused any symptoms. On one occasion the discomfort appeared soon after reading an upsetting letter. Recurrent pain while watching TV has now brought him to the Emergency Room. The pain disappeared about 15 min after it began, but by this time the patient was already on his way to the hospital.

What has happened to CAPT Green's chest pain? How does one characterize the changes?

What is the pathophysiology implied by these changes? What new abnormalities might be responsible? How might these possibilities be checked out?

CAPT Green has the clinical features of "unstable angina". What is the prognosis (predicted patient outcome) for this condition? How does this prognosis differ from the prognosis for patients with stable angina? What changes have likely occurred and how can these be assessed? What do these changes suggest concerning CAPT Green's management?
CHEST PAIN: ENCOUNTER #3

CAPT Green was admitted to the Coronary Care Unit without further symptoms. Three hours later, however, the same dull, oppressive substernal chest pain returned. This time it was worse than it had ever been before, feeling as though "an elephant" were standing on his chest. He demonstrated his symptom by placing a tightly clenched fist on his sternum. The pain now radiated down both arms, into the anterior portion of the neck, and into the lower jaw. He was sweating profusely and had intense nausea, with some attempts at vomiting. He was also somewhat lightheaded. Despite all these symptoms, he continued to have an unusually slow pulse rate. An electrocardiogram showed new ST segment elevation in several leads.

How does this current chest pain resemble prior episodes in its clinical features and its pathophysiology? How does it differ?

Sweating, nausea, and slow pulse rate suggest autonomic (cholinergic) activation. This can occur with severe, prolonged myocardial ischemia (especially ischemia of the inferior wall of the left ventricle). If myocardial ischemia is responsible, what is implied about this patient's coronary blood flow and extent of coronary obstruction?

The ST segment elevation is indicative of transmural (full thickness) ischemia of the left ventricle and recent high-grade, perhaps total, occlusion of a coronary artery. How does this finding on the electrocardiogram support conclusions already evident on clinical grounds?

Additional common sources of acute chest pain include gastroesophageal reflux disease (GERD), pericarditis, and pulmonary embolism. An uncommon but concerning possibility is aortic dissection. Compare and contrast characteristic presenting symptoms and clinical features in each of these with those of CAPT Green.
Key Definitions and Distinctions

**Ischemia:** Insufficient flow of oxygenated blood to meet the metabolic demands of the respective tissue.

**Angina Pectoris:** Chest pain induced by myocardial ischemia.

  Typical angina: Chest pain that is worsened by exercise (exertion) and relieved by rest and is of the usual quality and location of angina, i.e. retrosternal, dull, with radiation to arm, neck, or jaw and is therefore highly likely to be due to myocardial ischemia.

  Atypical angina: usually refers to pain that has some qualities consistent with angina but also some qualities inconsistent with angina, i.e. unusual location, quality, or duration. This may (or may not) reflect myocardial ischemia.

  Non-anginal chest pain: chest pain that has no features suggestive of myocardial ischemia, e.g., sharp, focal, or pleuritic pain, possibly lasting hours and often unaffected by exertion.

  **Stable angina:** Angina that is not new (symptom present >4 weeks), reliably occurs only above a certain level of exercise, and is relieved rapidly with rest.

  **Unstable angina:** Angina that is new, occurs at lower workloads than previously, or begins to occur repeatedly at rest. Typically indicates an acute coronary syndrome is present.

**Acute coronary syndrome:** unstable angina possibly with evidence of acute myocardial ischemia or infarction. This syndrome is often associated with fresh clot in a coronary artery.

  **Myocardial ischemia:** focal injury to cardiac muscle cells (myocytes) due to reduced perfusion and oxygenation.

  **Myocardial infarction:** focal death of cardiac muscle cells (myocytes) and eventual replacement with scar due to a prolonged (>20 min) episode of ischemia.
PATHOPHYSIOLOGY OF ANGINA PECTORIS

Angina Pectoris and Myocardial Ischemia: Angina is a unique type of chest discomfort that signals the presence of myocardial ischemia. Angina often accompanies myocardial ischemia but may be absent in some patients despite the ischemia. Heart muscle (myocardium) is said to be ischemic when its cells receive too little blood flow (via the coronary vessels) to support normal metabolic activity. Since cardiac myocytes are heavily dependent on oxidative metabolism, ischemia will occur when coronary oxygen supply to a significant myocardial region falls behind local oxygen demand. Lacking the abundance of high-energy phosphates available only from oxidative metabolism, ischemic myocytes rapidly cease to contract and start to leak the ions essential for normal function. Loss of normal contractility in ischemic myocardium causes shortness of breath, fatigue, and, if the ischemic region is large, lowers blood pressure. Ischemia-related ion leakage and membrane dysfunction result in a characteristic upward or downward shift of the ST segment on the electrocardiogram (ECG or EKG) (see illustration).
Membrane dysfunction may also lead to a lethal rhythm disorder such as ventricular tachycardia or ventricular fibrillation. Ischemic myocardium releases metabolites, such as adenosine, that stimulate local sensory nerve endings. In most patients--but not all--these nerve-stimulating metabolites produce a characteristic substernal oppressive discomfort, which is termed angina pectoris. Thus, the occurrence of angina and its relief are closely linked to underlying myocardial ischemia: when angina occurs, the patient is having ischemia and may experience further ischemic contractile and electrical dysfunction; when (brief) angina is relieved, ischemia has ceased and its ominous adverse effects are mitigated.

**Myocardial Oxygen Consumption:** Oxidative metabolism of the myocardium changes dramatically with changing activity of the heart. Increases in ventricular systolic wall stress, contractility, and heart rate are particularly effective in raising myocardial oxygen consumption. At rest, the heart muscle consumes relatively little oxygen, releases a minimum of vasodilator metabolites to act on coronary arterioles, and, accordingly, receives minimal coronary blood flow (about 1 mL/min/g). During exercise, heart rate, systolic left ventricular pressure (= systolic blood pressure in the absence of aortic stenosis), and myocardial contractility each increase. For these reasons, myocardial oxygen
consumption rises steeply, stimulating local vasodilator release and creating a proportionate rise in coronary blood flow, which may increase up to 4-fold (to 4 mL/min/g). With return to rest, all of these changes reverse. In patients with stable angina, narrowed coronary arteries restrict maximum coronary flow (and maximum oxygen delivery) to certain regions of the myocardium. At a point determined by extent of artery obstruction, coronary flow cannot increase sufficiently to keep up with rising myocardial demand for flow. Thus, these patients have a ceiling level of activity. Exertion at or above this ceiling brings on a deficiency of myocardial perfusion, i.e., ischemia and anginal symptoms. The ceiling can shift in otherwise stable patients, possibly with minor variations in coronary vascular tone. Nevertheless, the concept of a stable ceiling for effort is very useful in evaluating anginal symptoms: dramatic, consistent drops in this ceiling often signal a progression in coronary obstruction (unstable angina) and major rises in the ceiling are expected with a procedure bringing relief of coronary obstruction. Exercise after a meal hastens the usual rise in heart rate and blood pressure. Since maximum oxygen delivery is reached sooner, exercise after a meal causes an earlier development of ischemic pain (postprandial angina). Exercise in a cold environment has a similar effect.

Coronary Blood Supply: Angina and other ischemic problems result from an imbalance of supply and demand for oxygen and nutrients. Stable angina, as just described, reflects fluctuating demand in the face of a steady restriction in supply to some regions of the heart. The supply side deserves further consideration:

Fixed Coronary Obstructions: Most occlusive lesions represent atheromatous buildup at specific sites within arteries. Coronary flow is not affected until a lesion (plaque) blocks at least 50% of an artery's luminal cross-section (lumen=the artery’s blood-filled interior space). At 50-70% artery blockage, maximum flow is diminished and ischemia is produced by large-scale increases in demand, e.g., strenuous exercise. The much lower flows normally present at rest are compromised only by more severe blockage— at least 90% loss of luminal area. Thus, angina at rest (angina decubitus) suggests subtotal or total blockage of a coronary artery. Effects of coronary arterial occlusion are sometimes mitigated by the development of collateral channels linking occluded artery segments to unoccluded arteries; usual collateral flow is modest and insufficient to prevent angina. Once 90% blockage has been reached, even a small added increase in blockage can threaten tissue-sustaining coronary flow at rest. Additionally, raised flow velocities through the narrowed lumen can damage endothelium and favor thrombosis. Thus, angina at rest is ominous—it may be a harbinger of worsened myocardial ischemia in the near future.
**Variable Coronary Obstructions:** Atherosclerosis favors constrictor responses in subjacent smooth muscle of the artery wall. In some patients, fixed obstruction can be worsened episodically by coronary artery spasm. This can lead to fluctuations in the intensity of exercise needed to induce angina. In a few patients, fixed atheromatous obstruction is minor and ischemia develops unpredictably with severe focal arterial spasm. This **vasospastic angina** is treated with vasodilators such as nitroglycerin.

**Other Supply Considerations:** Anginal symptoms are often worsened by oxygen-poor blood associated with anemia or hypoxia. Tachycardia (excessively fast heart rate) shortens diastole, the time when most coronary flow occurs. Congestive heart failure leads to raised ventricular filling pressures, thereby compressing coronary microvessels and reducing the pressure gradient that drives coronary flow. The abnormalities just listed can make ischemic symptoms appear with less effort, i.e., they reduce coronary vascular reserve. However, they rarely cause angina in the absence of occlusive coronary lesions. Other abnormalities can cause angina with little or no large-vessel (epicardial) coronary occlusion. Myocardial hypertrophy (heart muscle expansion due to hypertension, aortic stenosis, and other problems) can predispose to ischemia by failing to increase the number of coronary microvessels enough to match the increase in metabolically active myofibrils (microvascular angina). Aortic stenosis and aortic insufficiency predispose to ischemia by inducing hypertrophy and also by reducing coronary perfusion pressure. Aortic valve disease can produce typical anginal symptoms even in the absence of atherosclerotic coronary obstruction. This symptom indicates the degree of aortic stenosis is severe (“critical”) and the outlook for the unrepaired condition is poor.

**Acute Coronary Syndromes: Unstable Angina and Myocardial Infarction:** Atherosclerotic blockage progresses slowly by gradual accretion of plaque. Sometimes arterial obstruction increases rapidly due to plaque rupture with plaque hemorrhage and/or local intra-arterial thrombosis. Patients with this problem often have a dramatic rise in ischemic symptoms. For example, they may develop exertional angina or angina at rest for the first time or have a sudden decrease in the amount of effort needed to bring on ischemic chest pain. These conditions are termed unstable angina. Problems with newly-acquired or more frequent chest pain may be compounded by ischemic contractile dysfunction or rhythm instability. In many patients, ischemic symptoms stabilize or improve spontaneously due to dissolution of plaque thrombus or hemorrhage combined with coronary collateral formation. Thus, unstable angina can transform into worsened or unchanged, stable angina. In other patients, plaque thrombosis leads to more plaque thrombosis. Cycles of intracoronary thrombus formation and dissolution can cause prolonged instability of symptoms and heart function. Commonly, thrombi grow to produce total coronary blockade, imposing complete, long-lasting ischemia on myocardium supplied by the blocked vessel. Severe ischemia that persists over 20 min
results in a progressively larger region of myocardial infarction. Beginning within the innermost (endocardial) layers after 20 min of ischemia, a "wavefront of necrosis" moves steadily outward within the portion of the left ventricular wall supplied by the blocked coronary artery, reaching its full extent about 2-4 hours later (possibly much longer—up to 24 hours—with “stuttering” ischemia). Loss of contractile function is permanent in the necrotic zone. However, associated chest pain does not ordinarily last more than a few hours, probably because of damage to sensory nerves when much of the flow-deprived region becomes necrotic. In general, chest pain that persists unabated for hours and hours is either due to surviving portions of jeopardized cardiac muscle (reflecting partially restored or persistent perfusion of an ischemic region) or to noncardiac causes.

Patients who present to the Emergency Room with anginal discomfort but without classic ECG changes of myocardial infarction may later prove to have a myocardial infarction based on the detection of myocardial “biomarkers” (cell proteins such as troponin) released into the blood. Before complete biomarker data are available, one may not know whether or not a patient’s unstable angina has led to a myocardial infarction. For this reason, all patients (not just those with ECG abnormalities) presenting with new-onset exertional or rest angina are said to have acute coronary syndromes. Complete results for biomarkers and later ECGs will distinguish those who have had necrosis (and hence a myocardial infarction) from those who did not (and therefore had only transient myocardial ischemia or possibly a non-cardiac cause of chest pain).

Silent or Non-painful Myocardial Ischemia: Not all myocardial ischemia causes recognizable chest discomfort. Some ischemic patients, particularly those who are elderly or diabetic, have no chest pain at any time. Their ischemia becomes evident only as contractile dysfunction (dyspnea) or electrical changes (ST segment shift or arrhythmia). The long-term outlook may be the same or worse in these patients than in similar patients with typical ischemic chest pain. Even patients with painful episodes have many more periods of ischemia not leading to chest pain. The reason for this is unclear. Painless ischemia in these patients may be of insufficient intensity to stimulate a sensory response. Painless ischemic episodes may indicate a bad prognosis for those with advanced heart disease (e.g., extensive coronary disease and left ventricular dysfunction) and have little if any meaning for those with milder coronary problems.

PERICARDITIS--CARDIAC PAIN NOT DUE TO MYOCARDIAL ISCHEMIA

Another common cause of chest pain, this is often mediated by viral infection: coxsackie/echo-/adeno-/ and other viruses including HIV, varicella-zoster virus (VZV), or Epstein-Barr virus. Pericarditis is also associated trauma or with bacterial infection (typically post-surgical but possibly tuberculous), malignancy (metastatic lung, breast, lymphoma, others), connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis), and rarely vasculitis. Sterile inflammatory pericarditis can appear 2-4 days post-MI as a direct extension of the underlying infarct. It can also manifest, probably as an autoimmune phenomenon, weeks after myocardial infarction or cardiac surgery (Dressler’s syndrome); or it may occur consequent to significant radiation exposure to the mediastinum.
(e.g., for Hodgkin’s lymphoma). Pericarditis often presents with a sharp-quality chest pain that decreases when the patient is upright or leaning forward and increases when supine. Pericardial pain may also increase with inspiration or cough (“pleuritic pain”) due to traction on inflamed tissues. On physical exam, pericardial pain commonly features tachycardia and an audible friction rub. ECG may show characteristic changes—“diffuse” ST elevations (observed in many leads) and PR depression—and a pericardial effusion is frequently visible on an echocardiogram.

NON-CARDIAC CAUSES OF CHEST PAIN

Seeking potentially lethal etiologies of chest pain is a critical first step for any patient presenting with chest pain. Initial diagnostic assessment and triage focuses on identifying and managing serious and threatening cardiac etiologies (see Figure 1). However, many non-cardiac etiologies may closely mimic cardiac disorders on initial presentation. An expanded differential is often required to address the full spectrum of disease that may present with chest pain. Some of these are highly lethal and require prompt diagnosis and treatment to avert disaster.

Aortic Dissection: This is an acutely life-threatening source of chest pain. Left untreated, mortality is measured in hours to days. An acute proximal (ascending aorta) dissection carries a 1-2%/hr mortality in the first 48hrs and even distal (descending aorta distal to the origin of the subclavian artery) dissection mortality is approximately 10% at 30 days. Appreciating the clinical features enables the astute clinician to recognize and act quickly to maximize the patient’s chances of survival. Dissections classically result from a break in the aorta’s inner lining (intima) with entering blood painfully tearing aortic intima from the outer (medial and adventitial) layers, blocking branch arteries and creating a new pool or channel of blood flow within the torn aorta. Historical features may be variable and subtle. Patients commonly describe an acute onset of sharp, “tearing” sub-sternal chest pain that radiates posteriorly (to the back between the scapulae) and rarely, anteriorly in the mediastinum. Examination may show hypertension with asymmetric BP/pulses and if proximal aorta is involved, a murmur of aortic valve regurgitation due to tear (avulsion) of valve leaflets. Established risk factors for dissection cause damage or gradual deterioration of the middle (medial) layer of the aortic wall: hypertension, underlying connective tissue disease (may be undiagnosed!), congenital or acquired anatomic predisposition (bicuspid aortic valve, prior valve or aortic root repair), pregnancy, and trauma. Aortic imaging is critical with widened mediastinum sometimes seen on plain chest x-ray and a “false lumen” and other characteristic abnormalities revealed on highly-sensitive CT or MRI.

Pulmonary Embolism (PE): PE is a highly-diverse, commonly occurring thromboembolic phenomenon with significant morbidity and mortality. PE is commonly associated with a deep vein thrombosis (DVT) and results from subsequent embolization of the thrombus from the proximal leg. The diagnosis of PE is one of the most subtle and challenging in clinical medicine. Clinicians should be
familiar with the “classic” findings but fully aware that 1) such findings are often non-specific for PE and 2) most often, “classic” findings in PE are equivocal or absent. Patients may (or may not) show signs of DVT– commonly unilateral limb edema swelling/redness/warmth/pain. PE may result from a “provoked” venous thromboembolism (VTE), such as a prolonged period of immobility and venous stasis (long air flight/car travel/surgery/dependent position). Alternatively, many malignancies have been strongly associated with VTE, such as pancreatic cancer, possibly due to tumor release of thromboplastin. Pre-existing evidence of DVT may be absent. PE symptoms include pleuritic chest pain, which increases with deep inspiration such that patients take shallow, frequent respirations. Chest pain in PE may also be non-pleuritic, dull, and substernal like angina. Patients may feel weak, dizzy, and “washed out”; systemic blood pressure may be reduced. More subtly, patients may have sinus tachycardia, the most sensitive but least specific clinical finding of PE. Patients may be hypoxic (cyanotic) with rales/crackles on physical exam, or they may have profound dyspnea and tachypnea with few other physical findings. A pleural effusion may be detectable on physical exam and visible on chest x-ray or CT scan. QRS and T-wave abnormalities on EKG may indicate more significant physiologic impact from larger PE and are not sensitive for detecting PE. Additionally, echocardiogram can identify increased pulmonary artery pressures and right ventricular enlargement. Although d-dimer, a breakdown product of blood clots, is sensitive for PE, it has poor specificity and elevations appear in a long list of quite common conditions. CT angiography is both highly sensitive and specific, though it requires administration of contrast-material, which may be toxic to renal function. In cases when CT is contra-indicated, a lung ventilation-perfusion scan can be helpful. PE should be considered in the differential for any patient with otherwise-unexplained chest pain. The important consequences of PE will be discussed at length in the pulmonary section of this module.

Gastroesophageal Reflux Disease (GERD): This is a common complaint often confused with ischemic myocardial pain, although it usually has characteristics readily identifying its GI origin. It is mediated by a relaxed lower esophageal sphincter (LES), which loses competence and permits acid reflux into the esophagus. Although this reflux may be clinically silent, GERD patients often describe chest pain. Clarification of symptoms, particularly identifying its linkage to meals, body position, and diet, is often helpful in differentiating GERD from a more lethal cardiac etiology. GERD is typified as a burning, substernal ache a few hours after meals (though not always) and with recumbent positioning. The chest pain can be severe and debilitating. It often temporarily improves with milk and antacids; occasionally it does not! Some patients have GERD triggered by foods (e.g., citrus or tomato products) which relax the LES. Patients may endorse a sour reflux in the mouth (“water brash”) after sleeping or recumbent positioning though others are completely asymptomatic and do not have this. Patients may aspirate this reflux, inducing cough, asthma, and other respiratory complaints. Repeated forceful vomiting can lead to a painful “Mallory-Weiss” tear in the esophagus, a condition needing endoscopic diagnosis and subspecialty care. Further diagnostic assessment for GERD will be discussed thoroughly in module 5.
**Esophageal spasm:** Similar to GERD, the discomfort of esophageal spasms is often substernal and described as an intense “gnawing” pain that (unlike angina pectoris) increases with swallowing. These spasms are unrelated to physical effort. They may improve similarly to cardiac chest pain with sublingual nitroglycerin, as well as calcium-channel blockers. Diagnosis is confirmed with esophageal manometry. Full discussion of the pathophysiology/biomechanics are discussed in module 5.

**Peptic Ulcer Disease (PUD):** This GI source of pain is classically epigastric in presentation but may be perceived as substernal with an intense burning/ache. PUD is commonly associated with aversions to trigger/exacerbating foods or to a majority of dietary intake altogether. Pain from PUD can be associated with GI bleeding manifesting as hematemesis or black, tarry stools (melena – digested blood). PUD with concern for GI bleeding also requires thorough evaluation and commonly admission to the hospital. Full discussion of diagnostic assessment and treatment occurs in module 5.

**Pancreatitis:** Similar in location to PUD/GERD, pancreatitis-associated pain can also present beneath the sternum and deep in the upper (epigastric) abdomen with a posterior radiation common. Pain may be alleviated by leaning forward. Pancreatitis is often described with binge/excessive alcohol intake or pancreaticobiliary (gallstone or malignancy) obstruction, and lipase elevation +/- abnormalities in liver function tests. Right-upper quadrant ultrasound is indicated for further assessment. Details of pancreatitis will be discussed in module 5.

**Musculoskeletal (MSK):** The most common substernal painful MSK complaint is related to costochondritis. Others include osteoarthritis of the thoracic spine, other spinal disease, rib fracture, and VZV (herpes zoster). Costochondritis is associated with overuse and is not infrequently seen in military populations (who are at risk for acute changes in exercise regimens). The pain/discomfort is often focal, palpable, and reproducible. It may be induced by exercise. Although MSK etiologies are relatively common, it is important to consider cardiovascular risk factors before accepting at this as a final diagnosis. Rib pain requires careful history for suspected etiology (be conscious of potential domestic violence). VZV presents in a dermatomal distribution, heralded by by tingling, burning pain and can be debilitating even prior to eruption of vesicles by 24-48 hours. Prior history of varicella is important to make this diagnosis.

**Psych:** Anxiety is a very common problem that occasionally causes oppressive substernal chest discomfort. Typically, a young, otherwise healthy patient presents with “horrible chest pain” amidst significant life stressors. In cases of suspected anxiety, it is important to appropriately evaluate for risk factors or other findings suggestive of organic etiologies of chest pain. Exercise stress testing or other noninvasive methods may reassure the patient and his/her family. Chest discomfort from anxiety is rarely exertional (aerobic activity may be protective) and other triggers are commonly identified. After careful consideration for alternative diagnoses, arriving at a diagnosis of anxiety may be disconcerting for many patients. However, significant beneficial clinical response is attainable with appropriate cognitive-behavioral therapy modalities. Anxiety will be discussed in greater depth in the behavioral health session.
on insomnia.
Figure 1: A Diagnostic Approach to Chest Pain

**“CHEST PAIN”**

Focused Hx & Exam
PMH, SocHx
ECG, Imaging

**Findings concerning for “Cardiac” Chest pain?**

YES  NO

**“Cardiac” DDx**
- Acute Coronary Syndrome
  (ischemia vs infarction)
- Pericarditis
- Aortic Dissection

1) ECG, telemetry
2) Cardiac biomarkers – Troponins, CK (isotype MB)
3) Imaging* (cardiac CT/MR, echo, cardiac cath)
*cardiology consult

**“Non-Cardiac” DDx**
- Pulmonary – PTX, PE, Pneumonia
- GI – GERD, Esophageal spasm, Mallory-Weiss tear, PUD, Biliary dz, Pancreatitis
- MSK – Costochondritis, Rib fx, Spine OA
- Derm – Herpes zoster
- Psych - Anxiety

**General Tenets:**
1) Assess for risk of life-threatening (often cardiac) process:
   - establish “safety net”
   - apply outcomes-driven guidelines/processes
2) Evaluate for alternative causes
   - begin with highest clinical suspicion

**Findings concerning for “Cardiac” Chest pain?**

YES  NO

1) Additional Hx & Exam
2) Labs: cbc, bmp, lft, amylase & lipase
3) Imaging: cxr/rib/spine films; CT, MRI, U/S
4) additional studies: EGD*
*specialty consult
Returning to the introductory patient...

1) With no further information, one must assume the chest blow was significant, possibly injuring bone and internal structures—heart, lungs, and great vessels. One must immediately be concerned about contusion (bruising) or even tear or laceration of: a) a coronary artery, the myocardium, or the pericardium; b) lung parenchyma, vessels or pleura; c) aorta and great veins.

2) While injuries could be minor and inconsequential, the list just given should raise significant concern. Coronary or myocardial injury could lead to myocardial infarction, arrhythmia and/or cardiogenic shock, and death. Great vessel or coronary laceration could cause intrapericardial hemorrhage and cardiac tamponade, causing hypovolemic shock and death. Great vessel injury can also precipitate hemothorax and a bronchial tear can lead to pneumothorax, either initiating severe difficulties with ventilation and oxygenation.

3) Myocardial pain (coronary or myocardial injury) would likely be steady and anginal in character (dull, substernal, oppressive, radiating to neck and jaw, increased by effort and alleviated by rest). Pericardial pain is typically positional (worse when supine). Pain from non-myocardial structures—pleura, pericardium, bronchi, great vessels, muscles, and bony thorax—is “pleuritic,” i.e. it increases with inspiration or cough and decreases with expiration. Accompanying weakness, lightheadedness, or shortness of breath would be important in identifying the severity of any of the conditions just mentioned.

4) Initial exam should focus on physical exam: a careful assessment of vital signs looking for tachycardia, cardiac irregularity, hypotension, paradoxical pulse (indicating cardiac tamponade), respiratory rate and effort, and presence of pale, sweaty or bluish skin color (looking for incipient shock or cyanosis). The jugular veins should be assessed (see below) and carotid and other pulses checked. Careful percussion and auscultation of the lungs will help identify pneumothorax and hemothorax. Cardiac murmurs could signal heart valve damage and a gallop could show myocardial dysfunction. If the patient is stable, one can focus on his presenting pain. Pericardial pain is often accompanied by a cardiac friction rub. Chest wall tenderness might help localize musculoskeletal injury and bony deformity might suggest fracture. Such findings might favor (but their absence does not exclude) the possibility of internal injury.

5) Electrocardiogram would be a good early test, looking for ST segment shifts (coronary or pericardial injury), T wave abnormalities, or arrhythmia (suggesting myocardial injury). A chest x-ray would also be of immediate use to look for bony injury, air or fluid in the pleural spaces, and lung injury. If the patient is sufficiently stable, more advanced imaging can be employed: echocardiography to show pericardial space and myocardial function, CT or MRI to image all intrathoracic structures, and angiography for precise definition of vascular structures.
6) What if: Lightheadedness and cardiac irregularity might suggest a serious (possibly episodic) rhythm disorder due to myocardial ischemia or contusion.

7) Bulging neck veins would be highly suspicious of pericardial tamponade interfering with cardiac filling. This is often accompanied by paradoxical pulse, hypotension, and tachycardia. Alternatively, breathlessness and bulging neck veins could result from a tension pneumothorax. In this situation, air trapped in the pleural space from ruptured bronchi increases intrathoracic pressure, reducing venous return to the heart and causing distended jugular veins. Distinctive features on physical exam are hyper-resonance and loss of breath sounds on the affected side and tracheal deviation away from that side. Acute heart failure is another possible reason for distended neck veins.

8) A new heart murmur could be due to damage to mitral or aortic valve support structures (e.g., mitral valve chordae) with resulting acute valve leakage.
Practice questions (and answers):

1. A 54 year old male presents to the Emergency Department with “crushing” chest pain and diaphoresis. If you are considering a diagnosis of unstable angina, and you learn that his chest pain is relieved with activity, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely

2. A 54 year old male presents to the Emergency Department with “crushing” chest pain and diaphoresis. If you are considering a diagnosis of pericarditis, and you learn that his chest pain is worsened with lying supine and with coughing and deep inspiration and he also has a low grade fever, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely

3. A 54 year old male presents to the Emergency Department with “crushing” chest pain and diaphoresis. If you are considering a diagnosis of unstable angina, and you learn that his chest pain came on with less activity than prior chest pain episodes and now continues while he is at rest, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely
**Answers**

1. B. Learning that the chest pain is relieved with activity makes the clinical scenario much less consistent with typical angina, which should worsen with activity by definition. Chest pain relieved with activity or physical exertion is referred to as non-anginal chest pain. Given this clinical presentation carries some descriptors that may be consistent with angina, this clinical presentation is best classified as atypical angina.

2. A. Each of the additional findings are typical for patients experiencing pericarditis. Additional clinical features of pericarditis include tachycardia, an audible friction rub and ECG may show characteristic changes —“diffuse” ST elevations (observed in many leads) and PR depression. On echocardiogram, a pericardial effusion is frequently visible and can be used to aid in the clinical diagnosis if there is diagnostic uncertainty.

3. A. This is consistent with unstable angina and increases the likelihood of the diagnosis. Unstable angina includes chest pain associated with myocardial ischemia and is defined as angina that is new, occurs at lower workloads than previously, or begins to occur repeatedly at rest. Unstable angina falls within the spectrum of Acute Coronary Syndromes, and should be cared for with appropriate urgency and attention.
Chest Pain case discussions

Small group case discussions are designed to follow immediately after oral case presentations and preceptor feedback in each preceptor-led small group.

In small group sessions, your preceptor will facilitate a discussion of key clinical aspects in each case. The goals of each small group are to develop clinical reasoning skills as the fundamental building blocks of clinical medicine. These goals are achieved via the following objectives independent of the content specific objectives:

1) Illustrate major diagnostic entities (common and/or serious) for the topic.
2) Describe typical patterns of presentation for these diagnostic entities (classic or typical patterns)
3) Construct a prioritized problem list for each case
4) Create a relevant differential diagnosis for each case
5) Demonstrate clinical reasoning by justifying the differential diagnosis using key clinical information or decision points towards establishing the diagnosis
6) Reinforce use of proper medical terminology and pathophysiology germane to each case

Every small group is intended to be a learning environment where active participation is encouraged and supported with content and context-specific preceptor feedback. Preceptors will assess your clinical reasoning through active listening as you discuss problem lists, differentials, and management aspects for each case. Preceptors will use a number of techniques to encourage participation so they can observe and assess your clinical reasoning skills. Preceptors also model clinical reasoning in their approach to each case.

*It is worth mentioning again -- Without active participation, preceptors will not be able to assess your understanding of the cases or focus the discussion on necessary aspects of clinical reasoning to improve your clinical reasoning skills. For this reason, active participation is required!
Clinical Reasoning Small Groups

Pleural Effusion
Clinical Integrative Puzzle (CIP)

You are about to match the following diagnoses…

A. CHF
B. Lung Cancer
C. Nephrotic syndrome
D. Tuberculosis
E. Community-acquired pneumonia with para-pneumonic effusion
F. Systemic lupus erythematosis with pleuropericarditis

… with their representative

History
Physical Exam
Radiographic Data
Laboratory Data
Treatment

This exercise allows you to “compare and contrast”-- something you will do all of the time as physicians. The cases also serve to bring up important teaching points and discussion. Some ambiguity is intentional. Come to small group prepared to explain your reasoning. Good luck!

I. MATCH the MOST LIKELY diagnoses for each PATIENT HISTORY
1. A 30 year old with a history of tobacco abuse (40 pack years) presents with a several day history of fevers, chills, productive cough and dyspnea on exertion. Has also decreased PO intake (=nothing by mouth) with onset of symptoms and has lost 4 lbs unintentionally.

2. A 40 year old with a history of arthralgias presents with a several day history of dyspnea, chest pain, fevers and chills. Denies night sweats or change in weight. Has also had the onset of a rash in sun-exposed areas (photosensitivity) since symptom onset.

3. A 60-year-old presents with a several week history of worsening dyspnea with lying recumbent that is relieved with sitting up. He has subsequently slept on 4 pillows at night with resolution of symptoms. He also reports 5 lbs of unintentional weight gain and new onset of bilateral ankle edema. Denies F,C,and NS. (=fevers, chills, or night sweats).

4. A 50 year old with a history of prior intravenous drug abuse presents with a several week h/o drenching night sweats, 10 lb of unintentional weight loss, cough and dyspnea. He reports that he had several tours in Korea while on active duty.

5. A 60 year old with a longstanding history of diabetes mellitus presents with a several week history of weight gain and feeling “swollen” all over. Dyspnea on exertion. He has had 5 lbs of unintentional weight gain. Denies F, C,NS.

6. A 70 year old with a several week history of worsening dyspnea and cough. He reports a longstanding history of tobacco abuse - 2 packs per day for 30 years (=60 pack years) as well as 10 lb unintentional weight loss. He denies F, C, NS. Also complains of headaches.

II. MATCH the MOST LIKELY diagnosis for each PHYSICAL EXAM (one is used more than once)

(1) Vitals: T=100.5F HR=106 BP=130/78
HEENT (head, ears, eyes, nose, throat): dry mucous membranes
Neck: unremarkable
Heart: increased rate, regular rhythm, + rub, no murmurs, gallops
Lungs: rales, + rub, decreased breath sounds and dullness to percussion at lung bases bilaterally
Extremities: no c/c/e (cyanosis, clubbing, or edema)

(2) Vitals: T=98.2F HR=106 BP=100/70
HEENT: unremarkable
Neck: jugular venous distention to mandible
Heart: laterally displaced PMI (point of maximal impulse), distant heart sounds, increased rate, regular rhythm with no murmurs/rubs, + S3
Lungs: rales, decreased breath sounds and dullness to percussion at lung bases bilaterally
Extremities: 2+ lower extremity edema; pulses 1+

(3) Vitals: T=99.2F HR=96 BP=110/70
HEENT: Facial edema
Neck: prominent veins over neck and superficial chest
Heart: RRR with no M/R/G (regular rate & rhythm without murmurs,rubs,gallops)
Lungs: decreased breath sounds, dullness to percussion at bases
Extremities: Pulses 1+ in upper extremity, 2+ in lower

(4) Vitals: T=101 F HR=86 BP=160/70; Gen: ill-appearing
HEENT: unremarkable
Neck: unremarkable
Heart: RRR with no M/R/G
Lungs: decreased breath sounds, dullness to percussion at base; rhonci present
Extremities: no c/c/e

(5) Vitals: T=98F HR=96 BP=160/70
HEENT: peri-orbital edema
Neck: normal
Heart: RRR with no M/R, + S4
Lungs: Bibasilar rales, decreased breath sounds, dullness to percussion at base
Extremities: 2+ lower and 2+ upper extremity edema; all pulses 2+

III. Indicate whether a pleural effusion from each of your diagnoses will MOST LIKELY be an EXUDATE or a TRANSUDATE.

CHF
Lung Cancer
Nephrotic syndrome
Tuberculosis
Community-acquired pneumonia with para-pneumonic effusion
Systemic lupus erythematosis with pleuropericarditis
IV. MATCH the MOST LIKELY diagnosis for each radiographic image(s).

1.

2.
V. MATCH the MOST LIKELY diagnosis for each pleural fluid cytology (microscopic analysis) (one is used more than once).

(1) Just a few scattered cells, mainly mononuclear - macrophages and mesothelial cells, lymphocytes and a few non-degenerated neutrophils

(2) Many white blood cells, majority are lymphocytes, and there are large, blue, cohesive epithelial cells seen in clusters/balls

(3) Many white blood cells, majority are lymphocytes, with a paucity of mesothelial cells

(4) Many white blood cells, majority are neutrophils, and the following is seen:

(5) Many white blood cells, majority are neutrophils, and the following is seen:
VI. Match the MOST LIKELY DIAGNOSIS for the following serum (blood) test and urine test results. ABNORMAL values are in BOLD TYPE. Normal values also provided and end of this packet.

(1) LAB DATA
Complete blood count
  **White blood cells** 16,000/mm³, 81% neutrophils, 10% bands, 9% lymphocytes
  **Hemoglobin** 11 g/dL
  **Platelets** 480,000/mm³
Serum electrolytes:
  Sodium 138 mEq/L
  Potassium 4.2 mEq/L
  Bicarbonate 21 mEq/L
  **BUN** 16 mg/dL
  Creatinine 1.1 mg/dL
  Calcium 7.9 mg/dL
  Albumin 3.5 g/dL
Other: None
Urinalysis Normal

(2) LAB DATA
Complete blood count
  White blood cells 11,000/mm³, 58% neutrophils, 2% bands, 33% lymphocytes
  **Hemoglobin** 15 g/dL
  **Platelets** 380,000/mm³
Serum electrolytes:
  **Sodium** 135 mEq/L
  Potassium 4.2 mEq/L
  Bicarbonate 21 mEq/L
  **BUN** 24 mg/dL
  **Creatinine** 1.6 mg/dL
  Calcium 7.9 mg/dL
  Albumin 3.5 g/dL
Other: **pro-BNP** 300 pg/mL
Urinalysis Normal

(3) LAB DATA
Complete blood count
  White blood cells 11,000/mm³, 58% neutrophils, 2% bands, 33% lymphocytes
  **Hemoglobin** 15 g/dL
  **Platelets** 380,000/mm³
Serum electrolytes:
  Sodium 141 mEq/L
  Potassium 4.2 mEq/L
  Bicarbonate 21 mEq/L
  **BUN** 16 mg/dL
Creatinine 1.6 mg/dL  
Calcium 7.9 mg/dL  
Albumin 3.5 g/dL  
Other: Anti-nuclear antibodies 1:640 dilution  
Urinalysis Normal

(4) LAB DATA  
Complete blood count  
White blood cells 11,000/mm3, 58% neutrophils, 2% bands, 33% lymphocytes  
Hemoglobin 11g/dL  
Platelets 380,000/mm3  
Serum electrolytes:  
Sodium 129 mEQ/L  
Potassium 4.2 mEQ/L  
Bicarbonate 21 mEQ/L  
BUN 16 mg/dL  
Creatinine 1.2 mg/dL  
Calcium 12.9 mg/dL  
Albumin 3.5 g/dL  
Other: None  
Urinalysis Normal

(5) LAB DATA  
Complete blood count  
White blood cells 11,000/mm3, 58% neutrophils, 2% bands, 33% lymphocytes  
Hemoglobin 15g/dL  
Platelets 380,000/mm3  
Serum electrolytes:  
Sodium 141 mEQ/L  
Potassium 4.2 mEQ/L  
Bicarbonate 21 mEQ/L  
BUN 16 mg/dL  
Creatinine 1.5 mg/dL  
Calcium 6.9 mg/dL  
Albumin 1.5 g/dL  
Other: None  
Urinalysis 1200 mg/24 h

(6) LAB DATA  
Complete blood count  
White blood cells 13,000/mm3, 81% neutrophils, 10% bands, 9% lymphocytes  
Hemoglobin 8.6 g/dL  
Platelets 230,000/mm3  
Serum electrolytes:  
Sodium 138 mEQ/L  
Potassium 4.2 mEQ/L
VII. MATCH the MOST APPROPRIATE DIAGNOSES for each of the following TREATMENTS (all patients would undergo additional evaluation and supportive care as well).

1) Levofloxacin

(2) Cisplatin or Gefitinib

(3) Lisinopril, furosemide, prednisone

(4) Isoniazid, PZA, ethambutol, rifampin

(5) Lisinopril, furosemide, beta-blocker

(6) Prednisone
<table>
<thead>
<tr>
<th><strong>USMLE Step 1 Laboratory Values</strong></th>
<th><strong>REFERENCE RANGE</strong></th>
<th><strong>SI REFERENCE INTERVALS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD, PLASMA, SERUM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Alanine transaminase (ALT), serum</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>* Aspartate transaminase (AST), serum</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>* Bilirubin, serum (adult) Total // Direct</td>
<td>0.1-1.0 mg/dL // 0.0-0.3 mg/dL</td>
<td>2.1-17 μmol/L // 0-5 μmol/L</td>
</tr>
<tr>
<td>* Calcium, serum (Ca²⁺)</td>
<td>8.4-10.2 mg/dL</td>
<td>2.1-2.8 mmol/L</td>
</tr>
<tr>
<td>* Cholesterol, serum</td>
<td>Rec&lt;200 mg/dL</td>
<td>&lt;5.2 mmol/L</td>
</tr>
<tr>
<td>Cortisol, serum</td>
<td>0800 h: 5-23 μg/dL // 1600 h: 3-15 μg/dL</td>
<td>138-435 nmol/L // 82-413 nmol/L</td>
</tr>
<tr>
<td>Creatinine, serum</td>
<td>Male: 25-90 U/L</td>
<td>Female: 10-70 U/L</td>
</tr>
<tr>
<td>* Creatinine, serum</td>
<td>0.6-1.2 mg/dL</td>
<td>0.53-1.06 μmol/L</td>
</tr>
<tr>
<td>Electrolytes, serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (Na⁺)</td>
<td>136-145 mEq/L</td>
<td>136-145 mmol/L</td>
</tr>
<tr>
<td>Potassium (K⁺)</td>
<td>3.5-5.0 mEq/L</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Chloride (Cl⁻)</td>
<td>95-105 mEq/L</td>
<td>95-105 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate (HCO₃⁻)</td>
<td>22-28 mEq/L</td>
<td>22-28 mmol/L</td>
</tr>
<tr>
<td>Magnesium (Mg²⁺)</td>
<td>1.5-2.0 mEq/L</td>
<td>0.75-1.0 mmol/L</td>
</tr>
<tr>
<td>Estradiol, total, serum (in pregnancy)</td>
<td>24-28 wks // 32-36 wks</td>
<td>30-170 ng/mL // 60-280 ng/mL</td>
</tr>
<tr>
<td>28-32 wks // 36-40 wks</td>
<td>40-220 ng/mL // 80-350 ng/mL</td>
<td>140-760 nmol/mL // 280-1210 nmol/mL</td>
</tr>
<tr>
<td>Ferritin, serum</td>
<td>Male: 15-200 ng/mL</td>
<td>Female: 12-150 ng/mL</td>
</tr>
<tr>
<td>Follicle-stimulating hormone, serum/plasma</td>
<td>Male: 4-15 mIU/mL</td>
<td>Female: premenopause 4-30 mIU/mL</td>
</tr>
<tr>
<td>Gases, arterial blood (room air)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>[14] 36-44 mmol/L</td>
</tr>
<tr>
<td>PCO₂</td>
<td>33-45 mm Hg</td>
<td>4.4-5.9 kPa</td>
</tr>
<tr>
<td>PO₂</td>
<td>75-105 mm Hg</td>
<td>10.0-14.0 kPa</td>
</tr>
<tr>
<td>* Glucose, serum</td>
<td>Fasting: 70-110 mg/dL</td>
<td>3.8-6.1 mmol/L</td>
</tr>
<tr>
<td>2-h postprandial: &lt; 120 mg/dL</td>
<td></td>
<td>&lt; 6.6 mmol/L</td>
</tr>
<tr>
<td>Growth hormone - arginine stimulation</td>
<td>Fasting: &lt; 5 ng/mL</td>
<td>provocative stimul: &gt; 7 ng/mL</td>
</tr>
<tr>
<td>Immunoglobulins, serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>76-390 mg/dL</td>
<td>0.76-3.90 g/L</td>
</tr>
<tr>
<td>IgE</td>
<td>0-180 IU/mL</td>
<td>0-0.380 kIU/L</td>
</tr>
<tr>
<td>IgG</td>
<td>650-1500 mg/dL</td>
<td>6.5-15 g/L</td>
</tr>
<tr>
<td>IgM</td>
<td>40-345 mg/dL</td>
<td>0.4-3.45 g/L</td>
</tr>
<tr>
<td>Iron</td>
<td>50-170 μg/dL</td>
<td>9-30 μmol/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase, serum</td>
<td>45-90 U/L</td>
<td>45-90 kU/L</td>
</tr>
<tr>
<td>Luteinizing hormone, serum/plasma</td>
<td>Male: 6-23 mIU/mL</td>
<td>Female: follicular phase 6-30 mIU/mL</td>
</tr>
<tr>
<td>20-30 U/L</td>
<td>5-30 U/L</td>
<td>7.5-150 mIU/mL</td>
</tr>
<tr>
<td>Osmolality, serum</td>
<td>275-295 mOsm/kg H₂O</td>
<td>275-295 mOsm/kg H₂O</td>
</tr>
<tr>
<td>Parathyroid hormone, serum, N-terminal</td>
<td>230-630 pg/mL</td>
<td>230-630 pg/mL</td>
</tr>
<tr>
<td>* Phosphatase (alkaline), serum (p-NPP at 30°C)</td>
<td>20-70 U/L</td>
<td>20-70 U/L</td>
</tr>
<tr>
<td>* Phosphorus (inorganic), serum</td>
<td>3.0-4.5 mg/dL</td>
<td>1.0-1.5 mmol/L</td>
</tr>
<tr>
<td>Prolactin, serum (hPRL)</td>
<td>&lt; 20 ng/mL</td>
<td>&lt; 20 μg/L</td>
</tr>
<tr>
<td>* Proteins, serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (recumbent)</td>
<td>6.0-7.8 g/dL</td>
<td>6.0-7.8 g/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5-5.5 g/dL</td>
<td>35-55 g/L</td>
</tr>
<tr>
<td>Glucagon</td>
<td>2.3-3.5 g/dL</td>
<td>2.3-3.5 g/dL</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, serum or plasma</td>
<td>0.5-5.0 μU/mL</td>
<td>0.5-5.0 μU/mL</td>
</tr>
<tr>
<td>Thyroidal iodine (³¹I) uptake</td>
<td>8%-30% of administered dose/24 h</td>
<td>0.08-30/24 h</td>
</tr>
<tr>
<td>Thyrotropin (TSH), serum</td>
<td>5-12 μg/dL</td>
<td>6.4-155 nmol/L</td>
</tr>
<tr>
<td>Triglycerides, serum</td>
<td>35-160 mg/dL</td>
<td>0.3-1.81 mmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₁), serum (RIA)</td>
<td>115-190 ng/dL</td>
<td>1.8-2.9 nmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₂) resin uptake</td>
<td>25%-35%</td>
<td>0.25-0.35</td>
</tr>
<tr>
<td>* Urea nitrogen, serum</td>
<td>7-18 mg/dL</td>
<td>1.2-3.0 mmol/L</td>
</tr>
<tr>
<td>* Uric acid, serum</td>
<td>3.0-8.2 mg/dL</td>
<td>0.18-0.48 mmol/L</td>
</tr>
</tbody>
</table>
PRO-BNP level <150 pg/dL
Introduction to Clinical Reasoning:

Dyspnea

William Kelly, MD

Acknowledgement: We would like to recognize Dr. Lisa Moores and Dr. Arnold Eliasson for their work on earlier versions of clinical reasoning course materials.

It’s 4 pm on a Friday and your last clinic patient comes in. He is a 40 year old male smoker with a three week history of “trouble breathing”. He also has a cough and some “swelling” in his feet. He has a history of “borderline” diabetes.

Questions:
1. What is his problem list?
2. What questions do you need to ask?
3. What should you look for on physical exam?
4. What causes of his dyspnea should you consider—because they are so common?
5. What are the most important causes to think about—because they are so serious?
6. What tests do you order?
7. Can the tests be done next week?
8. Or do you have to send him to the emergency department tonight?

Objectives:

Following the lecture and small group discussions, the student should:
1. Define and recognize how to characterize dyspnea
2. List a differential diagnosis for patients presenting with chronic dyspnea
3. List the historical, physical exam, and chest x-ray features associated with common life-threatening causes of acute dyspnea
4. List the initial testing useful in ALL patients with chronic dyspnea
5. Be familiar with selected tests used in difficult cases of chronic dyspnea
6. Apply the suggested diagnostic algorithm (schema) to representative clinical cases

Key definitions:

Dyspnea: Per American Thoracic Society (ATS) 1999 consensus statement, is “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”. And in 2012, they updated their guidelines and…. said the same thing! That may sound vague-- but it has to be. Much like thirst or pain, it is a “synthetic” sensation contributed to by many afferent pathways and experienced uniquely by different people.
See http://www.atsjournals.org/doi/full/10.1164/rccm.201111-2042ST#.U_pLosWwKuM for FREE full text of their official statement. We have all experienced dyspnea at some point and shortness of breath (SOB) can be normal with overexertion. However, when dyspnea occurs at rest or during exertion that is “less than expected”, it is pathologic and can reflect a serious underlying disease. 

**Chronic dyspnea:** Dyspnea that has been going on for *more than one month*. This is important, since *acute dyspnea (less than one month)* may be more likely to be imminently life threatening—for example with acute coronary syndrome or pulmonary embolism.

**Shortness of breath (SOB):** This is one description of dyspnea. Sometimes SOB may be used to imply more severe dyspnea including dyspnea at rest, and is distinguished from dyspnea on exertion (DOE).

**Orthopnea:** Dyspnea when lying down flat, which occurs with congestive heart failure “CHF” due to buildup of pulmonary edema fluid on the lungs. You can ask how many pillows the person sleeps on to gauge how significant it is. Keep in mind that gastroesophageal reflux disease (GERD) or post-nasal drip (PND) from allergies can also make people have to sleep upright.

**Paroxysmal nocturnal dyspnea (PND):** This is the more significant “PND” and refers to awakening at night suddenly due to short of breath. This is a more “specific” finding with CHF, meaning not everyone with CHF has it, but if a patient does have it, then it strongly suggests CHF. Obstructive sleep apnea (OSA), GERD, asthma or even vivid nightmares associated with post-traumatic stress disorder (PTSD) can also cause these episodes.

**Platypnea:** Dyspnea that worsens in the *upright position* (the opposite of orthopnea) may be related to “orthodeoxia” = a drop in arterial pO2 in the upright position associated with *arteriovenous malformations* or other right to left shunts and can be seen with advanced liver disease.

**BNP:** Brain (or “B-type”) natriuretic peptthree times a daye is a neuro-hormone synthesized by the myocytes (muscle cells) of the ventricles in response to pressure or volume overload and can be measured in the blood. A low level (<100 pg/mL) makes congestive heart failure very UNLIKELY. Values can be raised with congestive heart failure (CHF) but also pulmonary embolism and renal failure.

**Vocal cord dysfunction (VCD):** A condition in which the vocal cords close upon inspiration, in response to stress or other irritants, and can cause shortness of breath and wheezing. It may be mistaken for asthma or co-exist with asthma (perhaps 30% of the time). Diagnosis is suggested by the flow-volume loop chart made when a patient has pulmonary function tests done or by examining the vocal cords with a laryngoscope when they are having symptoms. Treatment is speech therapy as well as addressing any underlying triggers such as allergies, GERD, psychological stressors.

**Deconditioning:** Patients may have dyspnea because of sedentary lifestyle and weight gain. This is common but you must consider other causes since deconditioning is a “diagnosis of exclusion”. And be careful about assigning cause and effect—are they short of breath because they are out of shape? Or out of shape because dyspnea curtailed their ability to exercise? Activity should always be encouraged to try and interrupt this vicious cycle. **ADLs:** Activities of Daily Living, such as getting dressed or preparing meals. Sometimes dyspnea--- or any disability-- can be so severe as to impact these.

See additional **DEFINITIONS** in the Basic approach section.
Basic science highlights:

The brain stem and motor cortex along with multiple receptors in the upper airway, lungs and chest wall may all contribute to the sensation of dyspnea. The experience of dyspnea, however, also varies with the type of stimulus, situation, and the patient’s behavior and ability to find words to describe it. Dyspnea occurs when there is (1) an increase in respiratory drive or effort necessary to overcome an imposed load, (2) an increase in the proportion of respiratory muscle force required for breathing (the need to use “accessory” muscles), and/or (3) an increase in ventilatory requirements (due to anemia, thyroid disease, etc.). This “pathophysiologic” differential diagnosis (pathophysiologic approach using key findings as a clinical reasoning tool) is shown in Figure 1. This section will also illustrate basic patterns/disease presentations (or illness scripts), schemas (algorithms) and heuristics.

Basic approach to establishing the diagnosis:

Abraham Lincoln (1809-1865) is reported to have said “You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time”. Similarly, with dyspnea evaluations, all of your patients should have some basic tests, and some patients with especially challenging presentations may have all of the possible tests, but you should not do every test on everyone. More than half the time, the diagnosis is accurately determined based on just the history alone. If you combine history with physical exam and a chest x-ray, you will arrive at a correct diagnosis more than 80% of the time. Most patients should also get pulmonary function tests (PFTS) to assess for airway obstruction or restriction.

Begin by assessing the duration, quality and quantity of the symptoms. Classically, some descriptors have been associated with certain conditions (NEJM 1995):

Rapid Breathing: CHF, pulmonary vascular disease  
Incomplete Exhalation, heavy breathing, chest tightness: asthma  
Shallow Breathing: asthma, neuromuscular or chest wall disease  
Increased Work or Effort: COPD, interstitial lung disease (ILD), asthma, neuromuscular  
Feeling of Suffocation: COPD, CHF  
Air Hunger: COPD, CHF, pregnancy

Patients with vocal cord dysfunction (VCD) may describe a choking sensation and/or trouble getting air in. BUT it is important to note that several studies have failed to establish a clear association between any of the descriptors used and the underlying pathophysiology of the shortness of breath.

Timing of symptoms may be helpful as well. Is it positional (orthopnea, platypnea)? Is it intermittent (asthma, recurrent pulmonary emboli, cardiac ischemia) or chronic (COPD, pulmonary fibrosis)? And while exercise makes most causes of dyspnea worse, do symptoms increase after exercise-- as in exercise-induced asthma-- or are the present all the time (neuromuscular, mechanical or psychological problems).
Quantifying the dyspnea can help you better understand its impact on your patients’ daily life and also serve as a method of assessing improvement or progression over time or after treatment. You can ask the distance the patient is able to walk on a level surface, or the number of stairs the patient can climb prior to the onset of activity-limiting symptoms. There are several reproducible validated scales that have been developed for both regular patient care and research settings. See the addendum at the end of this note set for details.

The differential diagnosis of dyspnea in terms of pathophysiology is shown in Fig. 1. We can also approach the differential diagnosis of dyspnea by breaking it down by heart, lung or “other” (see Fig. 2, anatomic approach) which is helpful since two-thirds of the time there is a predominant cardiac or pulmonary etiology for the patient’s problem. Sometimes the cause is “multi-factorial” meaning there is more than one condition involved and you will have to address all of them in order to provide your patient with adequate relief. Below, several common and/or life-threatening causes of dyspnea are outlined for your review; key findings and pattern recognition (i.e. basic illness scripts) are emphasized in this section. Please review your recommended readings for further details.

**Congestive heart failure**

*Background:* One of the most common causes of dyspnea. 1.2% of the population has it and 80% of them are more than 65 years old. Risk factors include hypertension, coronary artery disease and smoking.

*History:* Dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, lower extremity swelling.

*Physical exam:* Edema, hypertension, increased jugular venous distension (bulging neck veins), murmurs or a “gallop” on cardiac auscultation (a third (S3) or fourth (S4) heart sound), hepatojugular reflux (HJR) (pressing down in the right upper quadrant of the abdomen (over the liver) causes increase in neck veins), “crackles” due to pulmonary edema heard when auscultating the lungs, and sometimes wheezing (also due to fluid in the lungs).

*Chest x-ray:* Will often show cardiomegaly and interstitial edema in the form of pulmonary vascular congestion, “Kerley B lines” or pulmonary effusions—all due to fluid backup into the lungs due to the poorly pumping heart.

*Additional testing:* Blood tests— serum brain natriuretic peptid three times a day (BNP) is a cardiac neuropeptide three times a day that is secreted by the ventricles in response to increased stretch. Values under a 100 pg/mL effectively rule out heart failure. The change in value over time can be used to monitor heart failure therapy. Of note, it can be falsely increased in patients with renal failure. Troponins are enzymes released by cardiac muscle when damaged and, if elevated, can suggest cardiac ischemia or infarction. Of note, both of these lab tests may be increased when the heart is damaged by another strain than can cause dyspnea, like pulmonary embolism.

ECG—may show infarction (ST elevation, Q waves, new left bundle branch block), ischemia (ST depressions or T wave changes), arrhythmias, “low QRS voltage” suggesting a pericardial effusion, or a tall QRS suggesting hypertrophied ventricle that has had to pump against blood pressure for a long time.
Echocardiography—Can measure the “ejection fraction” or efficiency of the heart muscle, check for ventricle wall motion abnormalities (indicates ischemia or infarction), heart valve problems, and pericardial effusions. Echocardiography is also a good screening test for pulmonary hypertension, which can cause chronic dyspnea, and can be due to heart failure and many other conditions.

Acute coronary syndrome

*Background:* Leading cause of death in the United States! You have less than two hours from initially seeing the patient to “reperfusion” of their heart with thrombolytic medications or cardiac angioplasty. Note that women and the elderly may have atypical symptoms, to include isolated dyspnea. Risk factors include age (males>45, females>55), diabetes, obesity, family history of heart disease, smoking, high LDL cholesterol or low HDL cholesterol.

*History:* Radiating chest pressure or pain, diaphoresis (sweating), and, of course, shortness of breath (SOB). SOB may precede chest discomfort or occur in absence of classic *angina pectoris.*

*Physical exam:* May have tachycardia. May see signs of heart failure (see above). Exam may be completely normal! Don’t be falsely reassured if you can “reproduce” the chest pain with palpation, since it may still be the heart and NOT musculoskeletal pain.

*Chest x-ray:* May demonstrate signs of CHF (see above) or be normal!

*Additional testing:* See blood tests, ECG and echocardiography - above.

Pulmonary embolism

*Background:* “one of the most commonly missed lethal diagnoses”. Afflicts 1:1000 Americans each year with a high mortality (35%). Risk factors include immobilization, surgery within the past three months, stroke, history of prior deep venous thrombosis or pulmonary embolism, and cancer. Other risks include recent extended travel, pregnancy or oral contraceptives use, family history, obesity and nephrotic syndrome (patient’s lose their anti-clotting proteins in the urine).

*History:* Sudden onset of SOB, syncope, pleuritic chest pain (pain worse with inspiration or coughing). May have fever. May have hemoptysis.

*Physical exam:* May have fever, tachypnea (breathing fast), tachycardia, hypoxia, hypotension. May have signs of right heart failure (pumping against the clot in the pulmonary arteries) to include distended neck veins and edema, a right sided S4 sound or increased pulmonic component to the S2. Check for signs of associated deep venous thrombosis to include edema, warmth, swelling and a “palpable cord” (which is the clotted vein) in the leg. “Homan’s sign” is of historical interest, and is pain in the leg when the foot is dorsiflexed, but it is not an accurate test. Physical exam can also be normal!

*Chest x-ray:* May be normal! Can show atelectasis (subtle decrease in lung size), effusions, infiltrates, and “classically” but only very rarely a “Westermark’s sign” which is a loss of pulmonary vasculature markings due to the “oligemia” or low blood flow beyond the clot, or “Hampton’s hump” which is a wedge or triangular shaped opacity (white area) that may look like a pneumonia and is due to an infarction or damage to the edge of the lung from decreased blood flow due to the clot.
Additional testing: A special CT scan of the chest (CT angiogram) is used to show the clots in the pulmonary arteries. D-dimer is a blood test that is usually elevated in patients with blood clots (but can be abnormal for other reasons like recent surgery or cancer, too). ECG may show “right heart strain” such as a new right bundle branch block or “S1Q3T3” which is a deep S wave in lead 1, Q wave in lead III, and T wave in V3 on the ECG, though this is uncommon.

Obstructive lung disease: COPD and Asthma

Background: Airflow obstruction and inflammation of the airways are a common cause of dyspnea. Asthma tends to afflict younger patients, often with allergies, with more “hyperactive” airways to a variety of stimuli. More than 1 in 20 Americans have asthma. COPD usually affects older people and most often is associated with tobacco smoking. It affects 20 million people in the U.S. and is the 4th leading cause of death.

History: Dyspnea, wheezing, chest tightness, and coughing. COPD patients also have purulent (pus) sputum. Quantify the number of “pack years” of smoking they have had. Symptoms may get better after use of a bronchodilator inhaler medication. Symptoms may be worsened with beta-blocker medications.

Physical exam: Asthmatic patients may have normal exams between episodes. When symptomatic they will have wheezing, a prolonged E- or expiratory- time to their breaths (usually a person takes just 1 second to breath in and two seconds to breathe out), “decreased” breath sounds due to poor air movement, use of “accessory muscles” like in the neck or abdomen to breath, and a “pulsus paradoxus” or drop in blood pressure more than 25 mm hg with inspiration due to increasing pressure within the chest. COPD patients may have a “barrel” chest due to air trapping and clubbing of the fingernails due to chronic hypoxia.

Chest x-ray: May show air trapping including flat diaphragms.

Additional testing: Pulmonary function tests are the only way to diagnose obstruction. The FEV1 (how much air they can forcibly expire in one second) and the ratio of this to the FVC (the forced vital capacity—how much total air they can force out) will be low (<70% for latter). In restrictive lung disease, all lung volumes are reduced (thus the name), but the FEV1/FVC ratio is greater than 70%. You can also check to see if an inhaler makes their lung function better.

Pneumonia

Background: Common. Elderly and immunocompromised patients may present with atypical or subtle symptoms.

History: Cough, purulent sputum (a “productive” cough), pleuritic chest pains, chills, myalgias (muscle aches).

Physical exam: Fever, “rhonchi” sounds on lung auscultation, increased “fremitus” (palpable transmission of the patient’s breath sounds).

Chest x-ray: “consolidation” or air-space disease in the area of the infection.

Additional testing: Blood testing may show an increased white blood cell count with band forms. You can also sample the sputum and blood for the bacteria and the urine for some “bacterial antigens”. Of course many nonbacterial pathogens can also cause infection in the lungs.
**Pneumothorax**

*Background:* May be spontaneous or due to a medical procedure or other trauma. Often due to underlying lung disease (emphysema, fibrosis).

*History:* Sudden onset of pleuritic chest pain not relieved with oxygen therapy.

*Physical exam:* Absent breath sounds. Sometimes tracheal deviation away from the side of the pneumothorax. There can be “hyper-resonance” to percussion between the ribs.

*Chest x-ray:* will show a thin white line (the pleura) and an absence of lung vascular markings between that line and the chest wall. If a patient is lying flat on their back, you may just see a “deep sulcus sign” which is a sharper and deeper-than-normal angle where the chest wall meets the diaphragm because air rises over the diaphragm in that area.

*Additional testing:* CT scan to look for underlying causes.

**Other**

As seen in the differential diagnosis lists, there is no shortage of other causes of dyspnea. Fortunately most will be discovered with your history, physical exam, and selected screening tests administered according to a logical algorithm (Fig. 4). Mechanical interference with breathing, as in pulmonary fibrotic (scarring) disorders or pleural effusions, anemia, renal failure, thyroid abnormalities, and toxins like carbon monoxide or aspirin poisoning can all cause dyspnea. Peripheral vascular disease and neuromuscular problems-- like a myopathy or myasthenia gravis—can also decrease exercise tolerance and give a sensation of shortness of breath. Psychiatric conditions including panic disorder can present with shortness of breath as well.

*Additional testing:* When history, physical exam, chest x-ray, pulmonary function tests and basic labs (e.g. hemoglobin, serum creatinine, and BNP) as well as any other tests indicated based on your evaluation, such as an echocardiogram, are negative, further testing IS available. It is called a “cardiopulmonary exercise test” (CPEX, CPET) and is a sophisticated measure of cardiac function, pulmonary gas exchange, ventilation and degree of physical fitness. Most often the patient rides on a stationary bike, while ECG and pulse oximetry are monitored, pulmonary function tests are done, and the oxygen consumed/carbon dioxide produced/and amount of air moved is recorded through a tight-fitting mask. Arterial blood is often sampled periodically from the wrist. Usually this allows identification of a cardiac, pulmonary or deconditioning limitation to exercise.

*Cardiac catheterization* may be performed if concerns are raised by ECG, ECHO or nuclear medicine functional imaging of the heart.

*High resolution CT scans (HRCT)* of the chest can occasionally be done to identify subtle interstitial lung disease, or fibrosis, that is not appreciated on chest x-ray. And very rarely, lung biopsy can be done in very difficult cases where such interstitial disease is still suspected.
Success of the algorithm (schema):

Several case series have been published and confirm the recommended algorithm for chronic dyspnea (Fig. 4).

Pratter et al (U Mass, Worcester) evaluated 100 consecutive patients referred to a pulmonary clinic (85 agreed to participate) with dyspnea of at least three weeks duration. Testing continued until a specific diagnosis was made (achieved in 100% of the cases). Tests included CXR, spirometry, bronchoprovocation testing, $D_1CO$ (diffusion capacity of carbon monoxide), cardiopulmonary exercise test, MUGA, 24 hour pH probe, and GXT (graded exercise stress test also known as exercise treadmill test or ETT). Specific diagnostic criteria were imposed and when good therapy existed, response to therapy was necessary to confirm diagnosis. They found:

- Asthma: 30%
- COPD: 14%
- ILD: 14%
- Cardiomyopathy: 11%
- Postnasal Drip: 7%
- Deconditioning: 5%
- Psychogenic: 5%
- GERD: 5%
- Cardiomyopathy: 11%
- GERD: 5%

DePaso et al (Seattle) evaluated 72 consecutive physician referred patients with dyspnea greater than one month unexplained by initial history, physical examination, CXR, and spirometry. A definite cause was found in 58 of 72 (80%) categorized into 22 diseases.

- Pulmonary disease: 3
- Hyperventilation: 1
- Cardiac disease: 1
- GERD: 3
- Extrathoracic disease: 1
- Poor Conditioning: 1

Both studies emphasize the utility of careful interpretation of radiographs and spirometry, as well as early use of bronchoprovocation and echocardiogram.

FIGURE 1


When thinking pathophysiologically, dyspnea can be due to:
- Mechanical interference with ventilation (like asthma, obesity, etc.)
- Weakness of the respiratory pump (neuromuscular disease, pneumothorax, etc.)
- Increased respiratory drive (heart failure, hypoxemia, renal disease, etc.)
- Wasted ventilation (large vessel obstruction or destroyed capillaries)
- Psychologic dysfunction

FIGURE 2
When thinking in terms of diagnoses, the most common ones are cardiac (heart failure, heart valve problem, etc.) and pulmonary (asthma, pleural effusion, pulmonary fibrosis, etc.). But about a third of cases are “non-cardiac, non-pulmonary” such as obesity, anemia, thyroid disease, and many more.

FIGURE 3
See “Table 2” History and Physical Exam Clues to Causes of Dyspnea. This is a key-features approach. From – Karnani NG et al. Am Fam Physician 2005;71:1529-37,1538.
FREE FULL TEXT AVAILABLE HERE:

FIGURE 4
FREE FULL TEXT AVAILABLE HERE:

In short, history and physical exam is followed by “level 1” testing, as indicated, such as screening for anemia, renal failure and taking a pulse oximetry, chest x-ray, ECG, etc. This will discover several common causes, which can then be treated. Failure to come up with a diagnosis leads to “level 2” testing (echocardiogram, more blood work, VQ scans, etc.). And, finally, “level 3” such as lung biopsy or cardiac catheterization.
Addendum: Dyspnea scales

There are several validated scales used to quantify and follow the degree of dyspnea, used for research purposes and also to monitor patients over time to see if they are getting better or worse with our interventions. These include the ATS shortness of breath, Modified Borg, and Visual Analogue Scale (VAS), shown below. The New York Heart Association Functional Classification-- while developed for patients with heart failure-- can also group patients with dyspnea based on their activity tolerance.

ATS Shortness of Breath Scale

<table>
<thead>
<tr>
<th>Descriptions</th>
<th>Grade</th>
<th>Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not troubled by SOB when hurrying on the level or walking up a slight hill</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Troubled by SOB when hurrying on the level or walking up a slight hill</td>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>Walks slower than people of the same age on the level because of SOB or has to stop for breath when walking at own pace on the level</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stops for breath after walking about 100 yds. or after a few minutes on the level</td>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>Too breathless to leave the house or breathless on dressing or undressing</td>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

Modified Borg Scale

10       Maximal
9        Very, Very Severe (almost maximal)
8        Very Severe
7        Severe
6        Somewhat Severe
5        Moderate
4        Slight
1  Very Slight
0.5  Very, Very Slight
0  Nothing at All

Visual Analogue Scale For Dyspnea*

Not Breathless ----------------------------------------------- Worst Possible Breathlessness

* The patient marks an “X” somewhere along the line to indicate how breathless they feel. The line is usually 10 cm length to facilitate calculation of result

New York Heart Association (NYHA)

Class I — No limitation during ordinary activity

Class II — Slight limitation by shortness of breath and/or fatigue during moderate exertion or stress

Class III — Symptoms with minimal exertion that interfere with normal daily activity

Class IV — Inability to carry out any physical activity; these patients typically have marked neurohumoral activation and muscle wasting.

And now, back to our patient…
It's 4 pm on a Friday and your last clinic patient comes in. He is a 40 year old male smoker with a three week history of “trouble breathing”. He also has a cough and some “swelling” in his feet. He has a history of “borderline” diabetes.

What is his initial problem list?
1. SOB
2. Cough
3. Lower extremity edema
4. Tobacco use (nicotine dependence)
5. Reported hyperglycemia

What questions do you need to ask him?
You would want to take a complete history with particular attention to certain things (key findings).
It has been going on for a while—but not that long—and he is still in that window of more acute onset (less than a month). Ask about the presence or absence of chest pain or pressure (which could represent myocardial infarction/ischemia in anyone, especially an older smoker). Chest pain could also indicate pulmonary embolism though he would not appear to have any risk factors for this. Ask about onset of symptoms. Did it start suddenly three weeks ago, or did it gradually build up over that time. If sudden onset, this may again suggest cardiac ischemia, pulmonary embolism or pneumothorax. Ask about CHF symptoms such as shortness of breath when lying flat (orthopnea), waking up at night with shortness of breath (paroxysmal nocturnal dyspnea) or leg swelling (edema). Ask about cough, and, if present, is it “productive” meaning producing sputum, or any blood. Maybe he does not have a cold now, but he had one last month, and now has “post-infectious” reactive airways disease/asthma. “Constitutional” symptoms, such as fever, night sweats and weight loss may imply chronic infection, cancer, or autoimmune disease.

What do you look for on physical exam?
You would start with vitals, to see if she was febrile (perhaps he could have pneumonia, but pulmonary embolism or cancer can also give you a mild fever), breathing fast (tachypneic) and, if you have one, a pulse oximeter to see if he is hypoxic. You will auscultate and percuss the lungs but don’t forget to look outside of the lungs—e.g., for signs of heart failure (distended neck veins, hepatojugular reflux, S3 gallop, and edema), or cancer (enlarged lymph nodes). Are there wheezes, rales or rhonchi on exam that may suggest obstructive lung disease, heart failure, or pneumonia, respectively?

What causes of his dyspnea should you consider—because they are so common?
Obstructive lung disease (asthma/COPD), especially given his smoking history, CHF,

What are the most important causes to think about—because they are so serious?
Acute coronary syndrome, pulmonary embolism.

What tests do you order?
Start with basics, such as blood sampling for a complete blood count (CBC) looking for leukocytosis (suggesting infection) or anemia, and electrolytes (checking for unsuspected renal failure). Consider a pro-BNP level (if low it is unlikely to be CHF) and thyroid function testing (thyroid stimulating hormone, or TSH and free T4). Check a chest x-ray, ECG, and, if available,
basic spirometry (pulmonary function). More advanced tests can then be ordered if you are still stumped, but remember, YOUR history, exam and a chest x-ray is all you need a majority of the time!

**Can the tests be done next week? Or do you have to send him to the emergency department tonight?**

Deciding if the patient is able to go home or has to come into the hospital (e.g. “patient disposition”) is an advanced skill you will practice throughout your training. For some conditions there are prediction tools/equations to help, but for the most part this is the “art of medicine” and you have to rely upon your instincts. Your initial testing above, may give you the answer, such as a concerning abnormal lab value or ECG showing cardiac ischemia. If the patient is ill appearing or in distress, or has an oxygen requirement (evidence of hypoxia with low pulse oximetry) or other abnormal vital signs, or has progressive symptoms, or-- for any number of reasons-- cannot be safely monitored/cared for at home or be able to come back in if he gets worse, then you should continue your evaluation in clinic or bring him in to the hospital.
Additional Practice Questions (and Answers)

1. The single most important element in determining the cause of dyspnea.

   a. History
   b. Physical exam
   c. Chest x-ray
   d. Pulmonary function tests

2-4. Match the disease “script” with the likely diagnosis.

   2. Smoker with dyspnea, wheezing, chronic purulent cough
   3. Sudden onset of shortness of breath three days after hip surgery. Chest x-ray is normal.
   4. Patient has rales on pulmonary auscultation bilaterally, and jugular venous distension is increased

   a) Pulmonary embolism
   b) COPD
   c) Vocal cord dysfunction
   d) Psychogenic
   e) Asthma
   f) Pneumonia
   g) Congestive heart failure
**Answers:**

1. The correct answer is A. The other tests are almost always done, but it is the history alone that most often reveals the correct diagnosis. So take a detailed one!

The answers are 2=B, 3=A, and 4=G. The “scripts” for the others would include-

C = throat tightness, wheezing, dysphonia, no or only partial relief with asthma medications

D = diagnosis of exclusion after extensive evaluation

E = similar to #2, and there is overlap, but asthma present in nonsmokers often and often allergen mediated, cough may or may not be productive

F = Subacute onset, often fever and purulent sputum
References


ICR Dypsnea Case Discussions

Case 1

A 25 year-old active duty Petty Officer presents with a chief complaint of dyspnea on exertion. He had been well all of his life except for seasonal allergic rhinitis that was relatively easily treated with antihistamines and decongestants. He first noticed his dyspnea several months previously when running in cold weather. He found his habitual running distance harder to cover in his usual time. His difficulty breathing was best characterized as tightness in his chest. He attributed his shortness of breath to "being out of shape". He had noted a 10 lb. weight gain since his wife gave birth to twins 8 months earlier, and to his inability to exercise as regularly as he used to. However, he also noted cough during his run, especially on colder days, and was sometimes awakened from sleep at night with cough, dyspnea and chest tightness. One of the main reasons he sought medical attention was that his wife was complaining that his cough awakened her at night, and she needed all the rest she could get. The patient was not sure he ever heard any wheezing but his wife sometimes remarked that she could hear "noisy" breathing.

Review of systems was positive for the 10 lb. weight gain. He denied chest pain, shortness of breath at rest, orthopnea, paroxysmal nocturnal dyspnea, sputum production, difficulty speaking and heartburn.

Past medical history was remarkable for a few doctor visits as a child for upper respiratory infections that were treated with a pink liquid medicine, a grape tasting liquid, and some kind of puffer medicine (inhaler) that he remembers using for a brief periods.

Social history reveals that he and his wife are nonsmokers. They have two cats that have been with the family for 10 years. The family has 4 members, including healthy twins born 8 months ago.

Family history reveals that the patient's father was a heavy smoker and died of some sort of lung disease. The patient's sister has asthma.

Physical examination shows a well-developed, somewhat overweight man with BP 124/76, P 70, and RR 16. Examination of the head, eyes, ears, nose and throat is normal. Chest auscultation reveals clear breath sounds with no wheezes on forced expiration. Expiratory time appears to be normal. Cardiac sounds are normal with no murmurs, rubs or gallops. Examination of the abdomen, genitalia and extremities is normal.

Laboratory data reveal a normal complete blood count and urinalysis. EKG shows a normal sinus rhythm with a rate of 74 beats per minute. Chest radiograph is normal. Pulmonary function data show a forced vital capacity of 4.3 L (95% of predicted), FEV₁ 2.8 L (75% of predicted), and FEV₁/FVC of 0.65. After albuterol, the FVC is 4.5 L (100% predicted), FEV₁ 3.2 L (86% predicted) and FEV₁/FVC 0.71. Arterial blood gas is normal.
Case 2

68 year-old man with chief complaint of gradually worsening dyspnea over the last 3 months. The patient's wife notes that he has "lost a step" regarding his breathing and that she hears gurgling breathing noises even when he is at rest. The patient has continued to play racquetball with his usual friends and has slowed down somewhat more than his friends have. He has had a dry cough over the last year but denies sputum production, chest pain, chest fullness or tightness.

Review of systems: He also denies fever, chills, sweats, change in appetite or weight change. He has no orthopnea, PND, or new pedal edema.

Past history includes: 1. hypertension controlled with lisinopril 40 mg daily, nifedipine 30 mg daily, atenolol 50 mg per day, furosemide 20 mg per day; and KCl 20 MEQ daily; 2. hyperlipidemia managed with simvastatin 20 mg at bedtime, niacin 500 mg daily; 3. diabetes mellitus for 8 years treated with metformin 500 mg daily, insulin SQ daily (NPH and regular, adjusted according to finger stick glucose measurements); 4. coronary artery disease, with 2-vessel CABG in 1996.

Social history includes former smoking, amounting to 50 pack-years, but no smoking since 1996. He lives with his wife in suburban Maryland and has been retired from the Air Force for 16 years. He travels only locally. He has no pets.

Family history is not available as he has no clear knowledge of his parents' medical histories.

Physical examination reveals a white man who appears his stated age, mildly dyspneic walking to the examination room. BP 130/90, P 90, R 18, T 98.4. Pulse oxygen 90% saturated at rest. The head, ears, nose and throat are normal. There is moderate A-V nicking in both fundi but no other remarkable findings in the eyes. There is no adenopathy. There is mild JVD to 12 cm. Auscultation of the lungs reveals bilateral basilar crackles that do not clear with cough, and occasional bilateral expiratory wheezes. There is no consolidation. Heart sounds include a normal SI and S2 and a 2/6 systolic ejection murmur at the left sternal border. The abdomen is soft, nontender and without masses. There is no clubbing, cyanosis or edema.

Laboratory data reveals normal chemistries, complete blood count and urinalysis. EKG shows a normal sinus rhythm with a rate of 90 beats per minute, and Q waves in the inferior leads. Pulmonary function tests show a forced vital capacity of 2.32 L (54% of predicted), FEV1 1.85 L (56% of predicted), and FEV1/FVC of 0.80. Chest radiograph shows hypoinflation, median sternotomy wires, and borderline enlargement of the cardiac silhouette. There are bilateral increased linear interstitial markings.
Case 3

The patient is a 28 year-old woman, an active duty medical officer who is air-evacuated to your facility for a medical evaluation board (MEB) for chronic, persistent asthma. MEB's are not authorized at the home medical institution so transfer to your facility was arranged to accomplish this administrative task. The patient's asthma began while she was in medical school and has been physically very limiting and poorly responsive to medications. She presented to an emergency department at age 24 with dyspnea and wheezing. She was initially treated with albuterol and a short burst of prednisone. Subsequently, acute exacerbations occurred at increasingly frequent intervals despite outpatient medications. She was admitted to the medical ICU on two occasions, intubated each time, but required only 24 hours of mechanical ventilation before her asthma attack broke. For outpatient management of her asthma, she was given an increasingly intensified regimen including fluticasone 220 ug - 2 puffs twice daily, salmeterol 2 puffs twice daily, ipratropium 4 puffs four times a day, and montelukast 10 mg daily. She also needed frequent courses of prednisone and was currently on a slowly tapering regimen at 10 mg daily. She was interested in getting the medical board done as quickly as possible as she wanted to get on with her residency training and felt very inconvenienced by the delay. She denied productive cough but often experienced loud wheezing. She noted that ever since she started using inhalers her voice sounded squeaky and there were times when she actually could not talk. She admitted a 20 lb. weight gain over the preceding year. She did not exercise at all, out of fear of precipitating an asthma attack.

Review of systems is positive for the 20 lb. weight gain. She denies chest pain, chest tightness, orthopnea, paroxysmal nocturnal dyspnea, sputum production, and heartburn.

Past medical history includes usual childhood illnesses.

Social history reveals that she is unmarried, is pursuing a medical career, and lives alone. She has no pets and no travel in the last 6 years.

Family history is noncontributory.

Physical examination reveals a well-groomed young woman with a pleasant demeanor and mild moon facies. Vital signs are normal. Examination of the head, eyes, ears, nose and throat is normal. Chest auscultation reveals clear breath sounds with no wheezes on forced expiration. Expiratory time is normal. Cardiac sounds are normal with no murmurs, rubs or gallops. Examination of the abdomen, genitalia and extremities is normal.

Laboratory data reveals normal blood chemistries, CBC and urinalysis. EKG shows a normal sinus rhythm. Chest radiograph is normal. Pulmonary function data show a forced vital capacity of 4.10 L (97% of predicted), FEV1 3.28 L (96% of predicted), and FEV1/FVC of 0.80. After albuterol, the values are unchanged. The flow volume loops show truncated flow and wavy, upsloping patterns.
Case 4

A 52 year-old woman complains of gradually worsening dyspnea over 6 months or more. (She is not exactly sure how long). She works part time in a clerical job but notices her dyspnea when doing work around the home, especially carrying laundry up a flight of stairs or making beds. She denies cough, mucus production, chest discomfort or chest fullness, fevers, chills, sweats, hemoptysis, orthopnea, PND, and pedal edema.

Review of systems is otherwise noncontributory except as in HPI and PMH.

Past medical history includes: 1. migraine headaches controlled with Midrin (infrequent in recent years); 2. remote history of recurrent urinary tract infections treated for a few years with suppressive nitrofurantoin; 3. menometrorrhagia and painful menses of many years' duration; 4. gastroesophageal reflux treated effectively with rabeprazole 20 mg daily.

Social history includes minimal social alcohol use and no tobacco use. She lives with her husband and adult son who has Down syndrome. Her family has two parrots but she does not care for the birds directly. She has traveled to Germany 6 months ago and generally goes to Europe every year or two.

Family history is positive for cancers, heart disease and diabetes.

Physical examination reveals a cooperative woman who appears her stated age. Vital signs include BP 116/80, P 90, R 12, T 98.0. Pulse oxygen 96% saturated at rest. The head, ears, nose and throat are normal. Her sclerae are pale but her eyes are otherwise normal. There is no adenopathy. Lung examination is normal. Heart sounds include a normal SI and S2 and a 2/6 systolic ejection murmur at the left sternal border radiating to the aortic region. The abdomen is soft, nontender and without masses. There is no clubbing, cyanosis or edema.

Laboratory data reveals normal blood chemistries. Urinalysis shows 5 RBC and 1 monocyte per high-powered field. Urine is nitrite negative. CBC shows a hemoglobin of 7.6 g/dL, WBC 11.1, platelet count 336,000. EKG is normal. Pulmonary function tests showed a forced vital capacity of 3.42 L (94% of predicted), FEV1 2.81 L (92% of predicted), and FEV1/FVC of 0.82. Chest radiograph is normal.
Introduction to Clinical Reasoning
Cough and Hemoptysis

William Kelly, MD

Acknowledgement: We would like to recognize Dr. Lisa Moores and Dr. Arnold Eliasson for producing earlier versions of clinical reasoning course materials.

Patient 1: A 38 year old female Army non-commissioned officer with a history of hypertension and cigarette smoking presents to your clinic with a complaint of three week history of dry cough. She feels as though she always has to “clear her throat”. The cough has interfered with her social life; she says, “People think I have tuberculosis or something”.

Questions
1. What is the initial problem list?
2. What other questions do you need to ask her?
3. What should you look for on physical exam?
4. What are the most likely possible causes for her cough?
5. What are the most serious possible causes for her cough?
6. Is the cough just due to her smoking?
7. Could it be the ACE inhibitor medicine she takes for her high blood pressure – even though she has been on that for a year before symptoms started?
8. Do you need to order any x-rays or tests?
9. Should you give her a medication for the cough? If so which one?

Patient 2: An 18-month-old girl with a chief complaint of “a cough.” The mother states she has been sick with runny nose for a couple of days, low grade fevers to 101.5F, and this “high-pitched cough,” which seemed to get much worse overnight last night. She has been breathing slightly faster than normal and hasn’t wanted much to eat or drink. She is an otherwise healthy girl with no significant past medical history. She is an only child and does attend daycare. Her immunizations are up to date.
Questions
1. What other questions do you need to ask the mother?
2. What should you look for on physical exam?
3. Do you need to order any x-rays or tests?
4. What special pathogens must you consider?
5. Should this child be treated? With what? And at home or in the hospital?

Patient 3: You are in Emergency Room evaluating a patient for admission when in the next room you hear a call for help. An elderly woman is coughing and with each cough has large volumes of bright red blood coming out of her mouth and nose. Her blood pressure is 180/30, heart rate 118, and her oxygen saturation on the monitor is mid 80%.

Questions
1. What do you do FIRST?
2. What tests do you need to order?
3. What is your initial treatment?
4. What is likely to be DEFINITIVE treatment?

Objectives: At the end of the session, the student will be able to
1. Identify the three most common causes of chronic cough.
2. Prioritize the likely diagnoses based on the history and physical examination.
3. Discuss the “empiric” approach to diagnosis and treatment.
4. Differentiate between hemoptysis and epistaxis and hematemesis.
5. Describe the pulmonary system blood supply and vessels usually the source of bleeding.
6. Identify major hemoptysis and what patients need hospitalization or ICU admission.
7. Identify the common and life threatening etiologies for hemoptysis
8. Outline a diagnostic approach for evaluating patients with hemoptysis

Cough: Key definitions and “pearls”:

Cough: a reflex action designed to clear the upper airways … and so much more

Chronic cough: cough lasting more than 8 weeks, implying that it not due to an acute infection, and for which the most likely causes are known and treatment algorithms are available (see below syllabus materials)

Acute and subacute cough: cough lasting less than 8 weeks, and most often self-limited and due to an acute infectious or post-infectious cause.

Productive cough: cough that results in the expectoration (bringing up) or mucous (phlegm).

Paroxysm: a “spell” or sudden onset, in this context used to describe coughing that occurs in rapid succession and progressively lower lung volumes, and can sometimes lead to emesis
(vomiting) because it is so intense.

Post-tussive emesis: Cough so severe that it ends in vomiting. Classically this has been associated with pertussis infection.

PND: Post-nasal drip, which may or may not be felt by the patient, which is oozing of secretions down the nasopharynx due to nasal or sinus inflammation from allergies or infection. Not to be confused with the other PND (paroxysmal nocturnal dyspnea).

UACS: Upper airways cough syndrome. The newer and better term for PND.

GERD: Gastroesophageal reflux disease. Acidic and non-acidic gastric contents can reflux into the esophagus and cause cough with or without aspiration into the lungs. Often, but not always, patients will have “heartburn” or “indigestion” or other symptoms. Sometimes you can see vocal cord erythema by endoscopy which may suggest GERD.

Eosinophilic bronchitis: A condition where eosinophils infiltrate the airways and cause cough. Like asthma, you can often detect eosinophils in the sputum and the treatment is inhaled steroids. UNLIKE asthma there is no “airway hyperactivity” or abnormal breathing tests.

Basic science highlights:

Anatomy: The cough reflex “circuit” is outlined in Table 1 below. With irritation of a cough receptor, impulses are transmitted along afferent nerves to a medullary cough center (“nucleus tractus solitarius”). Efferent nerves connect the cough center to the expiratory respiratory muscles which produce the cough. Note how many potential trigger sites (receptors) are NOT the lungs! Knowledge of these anatomic locations can help you understand the many causes of chronic cough.

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Afferent nerve pathway</th>
<th>Cough Center</th>
<th>Efferent nerve pathway</th>
<th>Effectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx Trachea</td>
<td>Vagus</td>
<td>Located diffusely</td>
<td>Vagus nerve</td>
<td>Muscles of Larynx and Tracheobronchial tree</td>
</tr>
<tr>
<td>Bronchi Ear Canal Pleura Stomach</td>
<td></td>
<td>in medulla, separate from but close to</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Physiology:** During the *inspiratory* phase of coughing, the patient takes a deep inspiration to a high lung volume which has the effect of straightening and lengthening the airways. In the *compressive phase*, the expiratory muscles contract against a closed glottis which generates a high intrathoracic pressure. The glottis is helpful but not absolutely required, since intubated patients (patients with a breathing tube down their throat) can still cough. During the *expiratory* phase, the glottis opens and there is a rapid, violent release of air. Expiratory muscles continue to contract to maintain high intrathoracic pressures and the diaphragm relaxes to allow pressures from the abdomen to be transmitted to the chest. The airways narrow which generates high flow rates, pushing any foreign material or mucous forward. The flow causes vibration which loosens any adherent mucous. Per the “equal pressure point theory”, high lung volumes cause dynamic compression of the larger airways. So a coughing paroxysm quite effectively first clears secretions from the larger airways and then shifts to the smaller airways as lung volumes are reduced.

**Basic approach to diagnosis and management:**

*Acting is merely the art of keeping a large group of people from coughing.*

**Sir Ralph Richardson** (1902 - 1983) *New York Herald Tribune, May 19, 1946*

Coughing is a natural, important defense mechanism that protects the airways from excessive mucous and foreign materials. Unfortunately it is also an effective means of transmitting infection. Cough is the *fifth most common symptom* seen in the outpatient clinic, accounting for 30 million physician visits and billions of dollars spent (often on ineffective cold medications) every year.

Fortuitously, the American College of Chest Physicians (CHEST) guidelines on the diagnosis and management of cough was just being presented at the time this clinical reasoning resource if being produced. Access at [http://journal.publications.chestnet.org/article.aspx?articleid=1892541](http://journal.publications.chestnet.org/article.aspx?articleid=1892541).

Estimates are that 15-20 % of the nonsmoking adult population suffers from a chronic cough at some time, and the incidence is considerably higher in smokers. A working knowledge of the common etiologies for cough and a systematic approach to patients is essential for both primary care providers and for specialists. You must be able to treat the most common causes, but also
exclude the most serious ones, in order to positively impact your patient’s health and quality of life. Complications of cough can include vomiting, rib fractures, urinary incontinence, syncope, muscle pain, tiredness, and depression.

This section of the syllabus will emphasize probabilistic approach to cough as well as illustrating key findings, patterns (illness scripts), and schemas.

There are many possible causes of cough, as shown below:

**Causes of cough**

**Irritants:** smoking or occupational exposures  
**Infections:** bronchitis, pneumonia (bacterial, viral, fungal, tuberculosis), aspiration pneumonia, pertussis  
**“Post-infectious”:** after any of the above  
**Lung diseases:**  
Airway diseases: asthma, COPD (chronic bronchitis), post-nasal drip (rhinitis, upper airway cough syndrome (UACS)), vocal cord dysfunction (VCD)  
Parenchymal disease (the lung tissue itself): interstitial lung diseases including pulmonary fibrosis, COPD (emphysema), sarcoidosis  
**Cardiovascular:** heart failure, pulmonary infarction, aortic aneurysm  
**Other diseases:** Gastroesophageal reflux disease (GERD), psychogenic (tic) cough, thyroid disease  
**Tumors:** bronchogenic (primary lung) cancer, metastatic (secondary) tumors, benign and malignant airway tumors  
**Foreign bodies:** aspiration, retained suture  
**Irritation of the external auditory canal** (via the auricular branch of the vagus nerve—also called Arnold’s nerve)  
**Drugs:** ACE-inhibitors

Extensive medical research has been done to see which of these causes are most common. The most common etiologies of chronic cough include **post-nasal drip** from a variety of causes (40-50% of patients), **asthma** (15-30%), and **gastroesophageal reflux** (10-20%). In patients with cough related to upper airway disorders, it is uncertain if the cough is from the post-nasal drip that accompanies these disorders or from direct stimulation of the cough receptors in the upper airway. Because of this, this syndrome has recently been renamed **Upper Airway Cough Syndrome (UACS)**. **Often (20-30% of the time) patients have MORE THAN ONE of these conditions.**

**History and physical examination** should focus on disorders of the organ systems associated with those afferent receptors (sinus disease, auditory canal, post-nasal drainage, gastroesophageal reflux symptoms, dyspnea and wheezing with exertion, aspiration). You should get a detailed history on the nature of the cough. However, unfortunately, neither the characteristics of the cough nor the presence or absence of sputum can be used to definitively rule in or out a specific diagnosis. Look for alarming symptoms or signs including chest pain, shortness of breath, hemoptysis, or “constitutional symptoms” like fever, night sweats, anorexia, weight loss, which may reflect a severe underlying infection, malignancy or systemic disease.
Ask about present and past smoking, occupational or hobby exposures, and medications.

*Chest x-ray* may have a “low yield” when ordered for patients with chronic cough who do not have other symptoms to suggest neoplasm or infection. That being said, I recommend a chest x-ray in older patients, smokers—and just about everyone.

*Pulmonary function tests* are typically done as part of the initial evaluation and can point to obstructive lung disease (asthma or chronic bronchitis/COPD) or suggest restrictive lung disease (like pulmonary fibrosis) as an etiology for the cough.

**Management:**

*Help your patient quit smoking:* One of the most common causes for a cough is cigarette smoking. Studies in smokers show that 1/2 of one pack-per-day smokers will have a chronic cough! The cough rate correlates with intensity of smoking. In addition, studies of children exposed to second hand smoke have shown a link between childhood coughing and smoking exposure so ask about this in pediatric patients that you see in clinic. Studies of smokers who quit suggest that the cough is directly related to smoking, since it disappears in over 3/4 patients, usually within a month of stopping smoking. Of course, myocardial infarction, stroke, emphysema and cancer prevention are all additional benefits of tobacco cessation. Many smokers presume their cough is due to smoking and will not seek medical attention, unless they have other symptoms, or the quality of the cough has changed and is concerning for infection or cancer.

**Chronic Cough: Approach to diagnosis:**

Several authors have published *algorithms (schemas)* for evaluating patients with a persistent cough, which have been tested in case studies, with diagnostic success rates in 85-99% range. First consider iatrogenic causes, particularly beta-blockers and angiotensin converting enzyme (ACE) inhibitor medications. *For patients with a clear etiology for the cough suggested by your history, physical exam or additional testing, then you can give specific therapy for that condition. Usually, however, no etiology (or multiple potential etiologies) is present. In this situation, empiric therapy is tried--this represents a probabilistic approach as the clinical reasoning tool for establishing the diagnosis.*

**Empiric treatment principles:**

1. Treat the most common likely condition first and then add treatment for the next most likely, and so on.
2. You cannot be sure of the diagnosis until the patient has responded to appropriate treatment for that diagnosis.
3. It can take *weeks to months* for a therapy to work. Most often a “treatment failure” is really an insufficient trial of therapy.
4. “Step down”, or stop treating some conditions, when your patient symptoms have resolved, as possible.

Treatment is first directed at the most common cause of cough -- upper airway cough syndrome (UACS). Patients with chronic rhinitis should receive nasal steroids and
antihistamine-decongestant combinations. Of note, this should be a “first-generation”
antihistamine. The newer, second-generation ones may claim to be less sedating, but they are
also much less effective! If there are signs/symptoms of sinusitis, you should order a sinus CT
scan and treated with antibiotics in addition to the medications listed.

After several weeks, if the patient has no response to therapy for an upper airway
disorder, look for asthma using challenge testing with methacholine, exercise or
hyperventilation.

Patients who do not have, or who do not respond to therapy for, upper airway disorders or
asthma may have **gastroesophageal reflex disease** (GERD). You can order a 24 hr. pH probe to
assess for this, but often patients will just be treated “presumptively” (again empiric treatment
without a firm diagnosis) with lifestyle modifications to include elevation of the head of bed, and
medications (proton pump inhibitors—i.e. omeprazole or prevacid). Therapy should be
continued for a prolonged period (at least 8 weeks) since resolution of the associated cough can be delayed.

At the end of the evaluation and treatment algorithm is **bronchoscopy**. For patients with
still no diagnosis after that, reevaluate with a careful environmental and occupational history and
a comprehensive otolaryngological evaluation. Repeating courses of treatment for UACS,
asthma, and GERD should be considered. **Psychogenic cough** is a “diagnosis of exclusion” and
requires an exhaustive evaluation and prolonged follow-up for diagnostic certainty.

**Summary:**

**Chronic cough** is common and can be debilitating. Sometimes it is associated with a severe
underlying disease. With attention to the history and physical examination, and a systematic
approach to diagnosis and treatment, you can bring relief to the overwhelming majority of your
patients. You must create a “therapeutic alliance” or partnership with your patients and make
them fully aware that the empiric, stepwise approach (heuristic), while most often effective, can
take a long time and that you will have to work together.

**And now, back to our patients...**

**Patient 1:** A 38 year old female Army non-commissioned officer with a history of
hypertension and cigarette smoking presents to your clinic with a complaint of three week
history of dry cough. She feels as though she always has to “clear her throat”. The cough has
interfered with her social life; she says, “People think I have tuberculosis or something”.

**What is the initial PROBLEM LIST?**
Sub-acute cough
HTN
Tobacco use/nicotine dependence

**What other questions do you need to ask her?**
You will take a complete history, but you want to focus on the nature of the cough. **Any rhinitis
or post-nasal drip sensation? Any dyspepsia (“heartburn”)?** Heartburn suggests
gastroesophageal reflux. **Any alarm symptoms such as hemoptysis, chest pain, shortness of
breath? Any fevers, night sweats or weight loss** that may suggest chronic infection (e.g.
tuberculosis), cancer or a chronic inflammatory disease like a vasculitis. **Any colds in the past**
six months? Perhaps it is a post-infectious cough or reactive airways disease. Any wheezing? This could suggest asthma or vocal cord dysfunction. Ask about smoking (past and present), occupational and hobby exposures to irritants, and medications.

**What should you look for on physical exam?**
You will listen to the lungs for wheezing, rhonchi or rales but don’t forget to also check the head and neck (e.g. rhinorrhea (nasal discharge), erythema or edema inside the nose, “cobblestoning” in the posterior oropharynx), lymph nodes in the neck supraclavicular area, and signs of congestive heart failure (CHF).

**What are the most likely possible causes for her cough?**
Upper airways cough syndrome (UACS)/PND, asthma, and gastroesophageal reflux disease are the most common—WHEN the chest X-RAY is normal! (an important heuristic to remember)

**What are the most serious possible causes for her cough?**
Consider cancer, especially in older patients and/or smokers, congestive heart failure, foreign body, obstructive lung disease (COPD).

**Is the cough just due to her smoking?**
Most patients who smoke have cough, and you should strongly urge her to quit smoking due to its many adverse health effects. Many smokers presume this is the reason for their cough and don’t come in to the doctor’s office unless there has been a change, so you should ask them why they came in at this time, and have a low threshold for considering cancer or infection. Don’t just assume a cough is just due to smoking and do nothing about it (an important heuristic!).

**Could it be the ACE inhibitor medicine she takes for her high blood pressure – even though she has been on that for a year before symptoms started?**
Yes, Yes and Yes. (important heuristic)

**Do you need to order any x-rays or tests?**
Guidelines vary. Since this is not truly chronic, yet, you might choose not to get a chest x-ray at this point, but ensure that the patient follows up with you in the near future so you can get one if the cough persists. In particular, if you are confident that asthma is responsible, you might forgo the chest x-ray, but I would have a low threshold for getting one if the patient has not had one recently. In this case, both her smoking and the reported severity of her cough support ordering an x-ray now. If she reported chronic symptoms or if there were other signs or symptoms of asthma, then pulmonary function tests would be appropriate.

**Should you give her a medication for the cough? If so which one?**
Her symptoms may suggest upper airway cough syndrome/post-nasal drip, and common things are common. So, if your history and physical and x-ray did not suggest something else, it would be reasonable to treat according to the provided algorithms, staring with a first generation antihistamine/decongestant, nasal saline rinses and nasal corticosteroids.

**Your next patient (approach to cough in pediatric patients)**
*Patient 2: An 18-month-old girl with a chief complaint of “a cough.” The mother states she has...*
been sick with runny nose for a couple of days, low grade fevers to 101.5F, and this ‘high-pitched cough,’ which seemed to get much worse overnight last night. She has been breathing slightly faster than normal and hasn’t wanted much to eat or drink. She is an otherwise healthy girl with no significant past medical history. She is an only child and does attend daycare. Her immunizations are up to date.

Questions

1. **What other questions do you need to ask the mother?**

   As in adults, cough is one of the most common chief complaints seen in children. In your approach to the pediatric patient with cough, your history and physical exam will be of utmost importance. As you take the history, it is important to understand if this is an acute (<2-3 weeks) or chronic (>2-3 weeks) cough. When does it occur? A chronic cough occurring in the early part of the night might suggest postnasal drip from sinusitis or allergies, while a dry cough in the middle of the night might be consistent with asthma. Cough after exercise could also suggest an asthmatic process and cough associated with meals warrants concern for gastroesophageal reflux. What does the cough sound like? A ‘barky’ cough is consistent with an upper airway process like croup or a foreign body, versus the throat-clearing cough of allergies or the ‘honking’ of a psychogenic cough (especially if it goes away at night).

   Are there other associated respiratory symptoms? Stridor (turbulent flow through large airways) is seen commonly in upper respiratory tract problems to include croup, foreign body, or anaphylaxis. Premature babies are more likely than term infants to have trachea or laryngeomalacia that might present with stridor. Additionally, premature infants have a higher likelihood of developing bronchiolitis. Has the child been febrile, suggesting an infectious etiology. What about sick contacts? What time of year is it? Bronchiolitis is much more commonly seen in the winter and early spring months. Asthma flares often occur with changes in seasons and concomitant pollutant burdens.

   Is there a family history of cough or asthma? For younger children, a detailed birth history might alert the practitioner to possible diagnostic clues. For infants, the differential diagnosis must include congenital anatomic irregularities to include vascular rings or slings, tracheoesophageal fistulas, airway hemangiomas, or tracheomalacia. Recurrent cough and infections in young children must raise suspicion for an immune deficiency to include cystic fibrosis.

2. **What should you look for on physical exam?**

   On physical exam, are there signs of respiratory distress to include tachypnea, subcostal or intracostal retractions, nasal flaring, or grunting? In infants and children, tachypnea (especially when associated with fever) is the most sensitive sigh of pneumonia. Are there crackles or rales, wheezing or rhonchi present? Bear in mind that it is common for children to have transmitted upper airway sounds audible over the lung fields. Are there signs of postnasal drip that could be contributing to the cough?

3. **Do you need to order any x-rays or tests?**

7:9
Additional studies, including laboratory and radiographic, might be warranted, especially if the child has signs of respiratory distress or is hypoxic. A leukocytosis, especially with a left shift, might point towards a bacterial pneumonia. A chest radiograph should be considered if pneumonia or a foreign body is suspected. Spirometry, in older children (usually five or older), might help with sorting out a chronic cough.

4. What special pathogens must you consider?

Finally, keep in mind a few pathogens that pose particular problems for infants and newborns. Additional viral tests for Respiratory Syncytial Virus (RSV) or Influenza might be warranted. While pertussis can cause disease and cough in adults, in infants it can be fatal and these patients often present with the classic spasmodic cough. The prevalence of this condition is much higher than it used to be in the population, as protection from its acellular vaccine wanes. Newborn infants can also develop pneumonia from Chlamydia Trachomatis.

5. Should this child be treated? With what? And at home or in the hospital?

Upon physical exam, your patient is slightly tachypneic with respiratory rates in the 40’s, and even at rest she has clearly audible stridor. Her oxygen saturation is in the low 90’s. She has some nasal flaring and some moderate subcostal retractions. Her cough sounds like a “barking seal,” and her lung fields are clear to auscultation. Your initial impression is this is a classic case of croup (laryngotracheobronchitis), but given her age and the relatively acute onset, you order a chest radiograph to rule out a foreign body aspiration. The chest x-ray is normal, but given her impressive stridor at rest and evidence of respiratory distress, you elect to admit this child for observation and treatment with corticosteroids and nebulized epinephrine treatments.

**Patient 3**: You are in Emergency Room evaluating a patient for admission when in the next room you hear a call for help. An elderly woman is coughing and with each cough has large volumes of bright red blood coming out of her mouth and nose. Her blood pressure is 180/30, heart rate 118, and her oxygen saturation on the monitor is mid 80%.

**Questions**

1. What do you do FIRST?

GET HELP! Call a “code blue” to activate your in-hospital emergency care team. This is massive hemoptysis by any definition and you have to act quickly in order to protect her from asphyxiating on the blood and/or becoming hemodynamically unstable due to blood loss. The patient needs to be intubated and have large bore IV access. Remember she is hypertensive because she has an adrenergic surge due to her respiratory failure. As soon as she is sedated for the intubation her blood pressure will drop – so have intravenous fluids ready on a pressure bag.
2. What tests do you need to order?
Certainly a “type & cross” so that you will be able to transfuse blood products is important. A complete blood count for the hematocrit level is important, but it may be falsely reassuring if normal. Acutely in bleeding, and when losing whole blood, the hematocrit may be relatively preserved. Check platelets and coags (PT, PTT) to see if there is a deficiency that must be replaced with platelet transfusion and/or fresh frozen plasma (FFP, clotting factors). A chest x-ray may show infiltrates on one side which would be a clue that THAT side is the one from which the bleeding is occurring.

3. What is your initial treatment?
Place the patient with the side of the chest that you think is bleeding facing down. This may help prevent spillage into the other lung. Give intravenous fluids (boluses of crystalloids) to maintain perfusion, and support with blood products.

4. What is likely to be DEFINITIVE treatment?
Pulmonary or critical care consultants may be able to do a bronchoscopy and, rarely, can do some intervention such as a tamponading balloon. However, definitive treatment will involve embolization of feeding lung blood vessels by interventional radiology using a catheter and/or a chest surgeon taking this patient to the operating room. Some diffuse alveolar hemorrhage syndromes require steroids and immunosuppression, depending on the cause.

References:


Hemoptysis

Definitions:

*Hemoptysis* - coughing blood from a source in the lower respiratory tract (below the vocal cords)

*Massive hemoptysis*: quantity of blood expectorated is sufficient to compromise respiration or gas exchange. Some of the definitions used to define are > 600cc over 48 hours, > 400 cc over 28 hours, >150-200 cc per episode. Patients with massive hemoptysis have a high mortality (more than 600 cc in 24 hours or 400 cc in 3 hours have > 75% mortality)

*Hematemesis* - vomiting blood from a source in the gastrointestinal tract. May be inhaled and then expectorated (coughed up) secondarily.

*Epistaxis* - Bleeding from the upper airway (usually nose)

Basic science highlights:

*Anatomy and physiology*: For hemoptysis to occur, by definition, there must be a connection between the airways and the pulmonary vascular system. The lungs are unique among the body's organs in that they have a dual blood supply (OK, so the liver has this, too).

(1) The pulmonary artery is a low-pressure, large volume circuit that circulates *deoxygenated* blood through the lungs and allows gas exchange to occur in the pulmonary capillaries. The **entire** cardiac output is cycled through the pulmonary circulation.

(2) The bronchial circulation is a high pressure, systemic circuit that provides oxygenated blood to the middle 85% of the lungs. The bronchial arteries arise from a wide variety of sources, including the aorta and intercostal, subclavian, innominate, internal mammary, and occasionally, coronary arteries. The bronchial circulation is typically 1 to 5 % of the cardiac output.

In conditions with chronic pulmonary inflammation, such as cancer, sarcoidosis, and tuberculosis, the bronchial arteries can hypertrophy, with significant increases in blood flow. Most hemoptysis is due to bleeding from the bronchial circulation, but significant hemoptysis from the pulmonary arteries and capillaries can occur in certain situations.

Basic approach to diagnosis:

Hemoptysis is common-- responsible for approximately 15 % of pulmonary consultations. While the overwhelming majority of patients with hemoptysis do NOT have a life threatening condition, it is very distressing to both patients and physicians and often indicates a serious underlying disorder.

This section of the syllabus will emphasize key findings and schemas (algorithms).
The first step is being sure that you are dealing with hemoptysis (and not a mimic).

**Differentiating between Hemoptysis, Hematemesis and Epistaxis**

<table>
<thead>
<tr>
<th>Hemoptysis</th>
<th>Hematemesis</th>
<th>Epistaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood is coughed up. There may be associated pharyngeal irritation. There may be an associated gurgling noise or sensation.</td>
<td>Blood is vomited, usually associated with retching and nausea.</td>
<td>Blood irritates the posterior pharynx and triggers a cough reflex. A sensation of inability to clear the throat is common, as is anterior nasal bleeding.</td>
</tr>
<tr>
<td>pH of blood is alkaline</td>
<td>pH of blood is acidic</td>
<td>pH of blood is alkaline</td>
</tr>
<tr>
<td>Blood is typically bright red</td>
<td>Blood is more commonly dark and often coffee-grounds in appearance.</td>
<td>Blood is typically bright red</td>
</tr>
<tr>
<td>Blood is frothy and mixed with mucus or pus</td>
<td>Blood is never frothy and may be mixed with food particles</td>
<td>Blood may be frothy and less commonly is mixed with mucus</td>
</tr>
<tr>
<td>Anemia less likely</td>
<td>Coexistent anemia from prior GI bleeding</td>
<td>Anemia less likely</td>
</tr>
<tr>
<td>Prior history of cough</td>
<td>Prior history of GI disturbance, liver disease, or NSAID use.</td>
<td>Prior history of nasal or sinus disease</td>
</tr>
</tbody>
</table>

There are *more than 100 different causes of hemoptysis* including cancer, infections, cardiac disease, vasculitis, trauma, and thromboembolic disease (pulmonary embolism). See a partial list below:

*Some Causes for Hemoptysis*

*Infection:* bronchitis, bronchiectasis, pneumonia, tuberculosis, parasites, fungi

*Cardiac:* congestive heart failure, mitral stenosis

*Vasculitis:* Wegener’s Granulomatosis, Lupus, Goodpasture's Syndrome, idiopathic hemosiderosis

*Pulmonary vascular disease:* pulmonary hypertension, arteriovenous malformations, thromboembolism, veno-occlusive disease

*Neoplasia:* bronchogenic carcinoma, bronchial adenoma, metastatic carcinoma

*Trauma*
Congenital: pulmonary artery hypoplasia/aplasia, sequestration, bronchogenic cyst
Iatrogenic: pulmonary artery catheter, bronchoscopy
Broncholithiasis: calcified “rocks” of lymph nodes from old infections (granulomatous disease) can sometimes erode into the airways
Factitious: patient is showing you blood from somewhere, someone or something else due to malingering or psychiatric illness

While the list of potential etiologies for hemoptysis is broad, most studies have indicated that the majority of cases are caused by only a few disorders. The most common causes worldwide are infectious, with Tuberculosis and Paragonamiasis, being the most common. In the United States, recent studies indicate a change in the etiology of hemoptysis. Older studies identified tuberculosis (25-40%), bronchiectasis (15-30%), and bronchogenic carcinoma (10-20%) as the most common causes. Results from four recent studies, including two from military hospitals are listed below:

<table>
<thead>
<tr>
<th>Causes for Hemoptysis</th>
<th>Johnson &amp; Reisz 148 patients (%)</th>
<th>O’Neil &amp; Lazarus 170 patients (%)</th>
<th>Sen, Walsh &amp; Bode 177 patients (%)</th>
<th>Santiago, Tobias &amp; Williams 264 patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>37</td>
<td>31</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Bronchogenic Carcinoma</td>
<td>19</td>
<td>10</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>7</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1</td>
<td>9</td>
<td>6</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Infection (other than TB)</td>
<td>10</td>
<td>0</td>
<td>----</td>
<td>12</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>22</td>
<td>4</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>43</td>
<td>25</td>
<td>22</td>
</tr>
</tbody>
</table>

“Miscellaneous” such as cardiac disease, coagulopathy, sarcoidosis, thromboembolic disease, and trauma make up a small portion of the causes.

You should remember that a significant bias is probably present in all of the published studies, since most use patients hospitalized or referred for subspecialty evaluation as the basis for their reports. Patients with mild, self-limited hemoptysis, and younger patients with a low risk of bronchogenic carcinoma are unlikely to be referred by their primary care physicians and are underrepresented in published studies.
The most important part of any evaluation of a patient with a complaint of hemoptysis is a careful history and physical examination. The history and physical exam are the keys to guiding you to the appropriate diagnosis and therapy. With such a broad differential, cost-effective medicine demands that tests be ordered based on appropriate clinical suspicion and in a way that triages patients most efficiently.

**History:**
- Quantity of hemoptysis (teaspoon, tablespoon, cup)
- Appearance (blood streaked sputum, bright red blood, frothy blood)
- Timing & duration
- Suspected location (patients can often identify the site of hemoptysis!)
- Associated symptoms (chest pain, fever, sweats, weight loss, cough, dyspnea)
- Prior episodes
- Other important historical factors
  - Travel
  - Occupational history
  - Prior TB exposure
  - Smoking history
  - Significant medical conditions (heart disease, diabetes)
  - Family history of bleeding, clotting disorders or connective tissue diseases (vasculitis)

**Physical exam:**
Usually unrevealing. Occasionally there will be signs of consolidation or collapse on lung examination. The cardiac examination is important to rule out congestive heart failure or significant mitral valvular disease. Clubbing, when present, signifies a chronic condition.

**Diagnostic tests:** See diagnostic tests below:

<table>
<thead>
<tr>
<th>Test</th>
<th>Situations where indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>All patients</td>
</tr>
<tr>
<td>CBC, platelet count</td>
<td>All patients</td>
</tr>
<tr>
<td>PT/PTT</td>
<td>? All patients</td>
</tr>
<tr>
<td>ABG</td>
<td>Any patient with suspected respiratory compromise</td>
</tr>
<tr>
<td>Chemistries</td>
<td>Suspected systemic disease, Admission to hospital for severe</td>
</tr>
<tr>
<td>UA</td>
<td>Vasculitis, pulmonary-renal syndrome suspected</td>
</tr>
<tr>
<td>AFB, fungal smear &amp; culture</td>
<td>TB/fungal infection suspected</td>
</tr>
<tr>
<td>Gram stain, culture</td>
<td>Infection suspected</td>
</tr>
<tr>
<td>ANCA, ANA, Anti-glomerular basement antibody</td>
<td>Vasculitis, Collagen Vascular Disease, Goodpasture's Syndrome suspected</td>
</tr>
</tbody>
</table>
Sputum cytology | At risk for lung cancer
---|---
Bronchoscopy | Most patients
CT scan* | At risk for thromboembolism and others (see below)
EKG/Echocardiogram | Suspected cardiac disease

*CT of the lung with standard chest protocol was evaluated in a small retrospective study (Haponik) of hospitalized patients. While CT identified more abnormalities than chest x-rays, there was little impact on management and CT was not routinely recommended. Another small prospective study (Millar) of chest CT in patients with 2 episodes of hemoptysis, a nonlocalizing chest x-ray, and a negative bronchoscopy found CT provided a diagnosis in 25% of the patients and provided additional information in another 25%. As a practical matter, most physicians WILL order a CT scan of the chest to look for a source of bleeding and/or to help guide bronchoscopy.

"Disposition" of the patient:
Where should the remainder of your evaluation take place? This is based on the severity of the hemoptysis, the patient's cardiopulmonary “reserve”—or how weak their heart and lungs are from other past diseases-- and the differential diagnosis considerations. In general, patients with massive hemoptysis, or suspected thromboembolism, vasculitis, or Goodpasture's syndrome are evaluated as inpatients.

Massive hemoptysis: Admit to a “monitored bed” (ICU). The most important immediate concern is control of the airway. Early intubation is recommended for patients who are at risk of respiratory compromise. When the bleeding site can be identified, the involved side should be placed down to minimize the risk of blood aspiration into the uninvolved lung. Cough suppression is controversial, but in situations where the cough appears to be causing ongoing irritation and bleeding, use of low dose narcotics may be helpful. Antibiotics should be started empirically in situations where infection is likely. Urgent bronchoscopy should be performed in an attempt to localize the bleeding site. All of these measures are unlikely to affect immediate control, however.

Older, retrospective, case-controlled studies comparing medical management with surgical intervention showed significantly higher mortality in the best medical care group. Among patients who were surgical candidates, medical management was associated with a 3-fold increase in mortality (Crocco).

Unfortunately, many patients with major hemoptysis do not have the pulmonary reserve for surgery, and many of the more common causes of massive hemoptysis are diffuse disorders (bronchiectasis, tuberculosis) or have a poor prognosis (bronchogenic carcinoma, metastatic carcinoma, cystic fibrosis). Since the overwhelming majority of patients with massive hemoptysis are bleeding from a bronchial arterial source, bronchial arterial embolization has become the standard modality employed to control bleeding. Bronchial arterial embolization establishes immediate control of bleeding in 75-90% of patients. The procedure involves identification of the bleeding vessel and selective canalization with a catheter. Steel coils or gel
foam, both of which cause clotting of the vessels, are injected. While this procedure spares lung tissue and works for most patients, approximately 20% of patients who have initial control will rebleed, usually within 6 months. Patients who fail embolization are candidates for endobronchial intervention, with a tamponade catheter or injection of fibrin glue or emergency surgery.

Moderate hemoptysis (30-100 cc per day): admit to the hospital for observation and an expedited evaluation. Bronchoscopy should be performed to localize the bleeding site. Specific therapy directed at the likely etiology should be instituted and consideration of embolization (for diffuse diseases) or surgery (for localized processes) is indicated. Prompt consultation to the thoracic surgeon and/or interventional radiologist should be part of the admission process for any patient admitted because of hemoptysis.

Minor hemoptysis: This subset represents the majority of patients seen with hemoptysis. Patients often present with blood-streaked sputum or small amounts (15-30 cc) of bleeding and usually can be evaluated and treated as outpatients. The most important diagnostic step in evaluating this subset of patients is the chest x-ray. Patients with a focally abnormal chest x-ray and without a clearly evident infection (pneumonia, lung abscess) should undergo diagnostic bronchoscopy. Patients with an obvious infection should be treated with antibiotics and followed closely. The patient with a normal or “non-focal” chest x-ray should be considered for further evaluation based on the following factors:

- Age > 40
- Male gender
- Tobacco use (> 40 pack years)

Patients with 2 or more of these characteristics should have bronchoscopy to rule out bronchogenic carcinoma. Studies involving over 450 patients have shown a rate of cancer of approximately 5% in patients with hemoptysis and a nonfocal/normal chest x-ray. Limiting bronchoscopy to the patients with the criteria listed above will identify the overwhelming majority of patients with lung cancer and reduce the number of procedures by 30-50%. Patients who do not undergo bronchoscopy should be watched closely and bronchoscopy reconsidered if hemoptysis persists or recurs.

A percentage of patients (in some studies 20-40%) will not have a diagnosis despite a thorough diagnostic evaluation. These patients should be reassured that their risk for developing cancer over the next several years is less than 2%. In numerous studies with over 400 patients, 1.6% of patients developed cancer, most commonly a solitary pulmonary nodule, probably unrelated to the hemoptysis.

Summary:
Hemoptysis is very distressing and has a broad differential diagnosis, but is most often due to active or past infection. Cancer is always a concern and should be investigated in patients at risk. All but minor hemoptysis requires hospitalization. Bronchoscopy is indicated in most cases, but it is usually arterial embolization done by interventional radiology and or surgery that is needed to stop the bleeding.
References


Figure One

Patient with Hemoptysis

- History, PE
- CBC, coags, ABG
- CXR
- Exclude: hematemesis, epistaxis

Severity of Hemoptysis

- Mild
  - Treat Infection, If present
  - Smoke
    - Abnormal CXR
      - Age ≥ 4
        - Recurrence
          - Bronchoscopy
    - Normal CXR
      - Age < 40
        - No recurrence
          - Observe

- Moderate
  - Admit for observation
  - Non-smoker
    - Normal CXR
      - Bronchoscopy
    - Abnormal CXR
      - Bleeding Stopped
        - Treat underlying disease
        - Consider embolization or resection

- Severe
  - ICU admission
  - Bleeding Continue
    - Observe
Practice questions (and answers)

1. The most common causes of chronic cough with a normal chest x-ray include post-nasal drip, gastro-esophageal reflux, and
   a. Asthma
   b. Habit, or tic, cough
   c. Congestive heart failure
   d. Lung cancer

2. If you decide to treat chronic cough empirically, you start with the most common etiology, which is
   a. Post-nasal drip
   b. Asthma
   c. Gastro-esophageal reflux
   d. Psychogenic

3. Cough, with unilateral (one side of body only) wheezing on pulmonary auscultation, suggests
   a. Asthma
   b. COPD
   c. Congestive heart failure
   d. Endobronchial lesion

4. All of the following should prompt you to recommend bronchoscopy for scant hemoptysis EXCEPT
   a. Age>40
   b. Female
   c. Tobacco use
   d. Constitutional symptoms

5. A history of post-tussive emesis increases the likelihood that THIS is the cause of chronic cough.
   a. GERD
   b. Pertussis
   c. Asthma
   d. Congestive heart failure
6. Cough, wheezing, shortness of breath that responds to inhaled corticosteroids but is associated with a NORMAL methacholine challenge is most consistent with
   a. GERD
   b. Eosinophilic bronchitis
   c. Asthma
   d. Foreign body

7. All of the following can INCREASE with chronic cough EXCEPT
   a. Incontinence
   b. Peak flow
   c. Syncope
   d. Intracranial pressure
Answers
1. The answer is A. The most common etiologies for chronic cough include *post-nasal drip, asthma*, and *gastroesophageal reflux*.

2. The answer is A. *Post-nasal* (40-50% of patients), *asthma* (15-30%), and *gastroesophageal reflux* (10-20%). In patients with cough related to upper airway disorders, it is uncertain if the cough is from the post-nasal drip that accompanies these disorders or from direct stimulation of the cough receptors in the upper airway. Because of this, this syndrome has recently been renamed *Upper Airway Cough Syndrome (UACS)*. **Often (20-30% of the time) patients have MORE THAN ONE of these conditions.**

3. The answer is D. Wheezing is usually bilateral from a diffuse process in all of the other diagnoses. The endobronchial lesion can be a tumor, mucous plug, or aspirated foreign body, but will manifest with lateralizing symptoms.

4. The answer is B. Male gender has been shown in retrospective analyses to be a risk factor, improving the yield of bronchoscopy. But females DO get lung cancer too, or may have indolent infectious causing hemoptysis.

5. The answer is B. A finding of post-tussive emesis minimally increases the probability that cough is due to pertussis.

6. The answer is B. Patients with reactive airways disease will have an abnormal methacholine test or other bronchoprovocation. Patients with eosinophilic bronchitis do not have this, but they still get better with inhaled steroids. Steroids would not be expected to help the other listed conditions.

7. The answer is B. Cough is associated with numerous adverse physiologic events because of the pressure swings. It has varied effects on peak flow meter readings and therefore PFTs should be repeated if cough interrupted the test.
Case 1

A 75 year-old retired Navy Captain complains of nonstop coughing for the past 2 months. She had been in her usual state of compensated health when she noted onset of a nonproductive cough without fevers, chills, nasal congestion, post-nasal drip or itchy eyes. She also denied hemoptysis. She characterized the cough as nagging and insistent, but not deep or severe. She thought the cough might be due to a flare in her rhinitis/sinusitis and she implemented her usual saline nasal lavages, Deconamine capsules, and fluticasone nasal spray. These measures seemed to help a little at first but after a couple of weeks of therapy she felt that the cough was no better. The cough annoyed her husband and the people all around her at Church.

Review of systems is positive for a mild sense of daytime fatigue that led her to take longer naps than she used to. She does report awakening feeling refreshed in the morning and after her naps, but she says she would "run out of steam" after several hours.

Past medical history is remarkable for numerous bouts of rhinitis and sinusitis treated vigorously over the years with antibiotics, decongestants, nasal steroids, expectorants, and a surgical procedure to open the ostium to one of her sinuses. Approximately 18 months previously, she had suffered a reversible ischemic neurological deficit (RIND) with no lasting neurological sequelae. Neurology had implemented stroke prophylaxis with simvastatin 20 mg per day and ramipril 5 mg per day, even though her BP and lipid panel were normal. She had no PMH of COPD, heart disease, diabetes, or other major illnesses.

Social history reveals that she and her husband are nonsmokers. They have three grown children and five grandchildren less than ten years old. She does not drink alcohol.

Family history is noncontributory.

Physical examination shows a well-developed, well-nourished white woman with BP 120/76, P 88, and RR 12. Examination of the head, eyes, ears, nose and throat is normal except for mild pharyngeal erythema. Chest auscultation reveals clear breath sounds with no wheezes or rhonchi. Expiratory time appears to be normal. Cardiac sounds include a normal S1 and S2 with no murmurs, rubs or gallops.
Examination of the abdomen is normal. There is no clubbing cyanosis or edema.

Laboratory data reveal a normal UA, CBC and chemistry profile. EKG shows a normal sinus rhythm with a rate of 84 beats per minute. Chest radiograph is normal. Pulmonary function data show a forced vital capacity of 3.60 L (95% of predicted), FEV1 2.89 L (94% of predicted), and FEVI/FVC of 0.80. Finger oximetry shows oxygen saturation of 96%.
Case 2

A 32 year-old man presents with chief complaint of "spitting up a bunch of blood". He had felt well until the day prior to arrival when, he produced approximately 1 cupful of bright red blood while singing in the shower. He states that he thinks the blood came from his chest because he could feel some gurgling in his chest prior to the production of the blood. He went to a local emergency center where a chest radiograph was taken and was read as normal. He was told to go home and rest. After being home for a couple of hours, he felt a warm gurgling in his chest and produced another 1 to 2 cups of bright red blood. He called central appointments and got an appointment in your clinic for today.

Review of systems: He denies recent URI, chest pain, dyspnea on exertion, chest trauma, leg pain or swelling, fever, chills or any other bleeding problems.

Past history includes an appendectomy at age 22. He was hospitalized for a lower gastrointestinal bleed (maroon-colored stools) of an ill-defined source at age 29. He required no transfusions and had no surgical intervention. He has no allergies and is currently on no medications.

Social history reveals that he has 2 children ages 4 and 8, in good health. He is an active duty Air Force Major and his wife does part-time volunteer work with the Red Cross. He does not drink nor does he or his wife smoke tobacco.

Family history is remarkable for a grandmother who had a chest operation at age 30 for a "big blood vessel". The patient's mother had active tuberculosis as a child. One brother has diabetes mellitus but there are no other familial diseases.

Physical examination reveals a well-developed, well-nourished, cooperative Hispanic man who produced another cup of bright red blood during the physical examination. BP 120/80, P 90, R 12, T 98.0. Pulse oxygen 95% saturated at rest. Head, eyes, ears and neck examination were normal. Examination of the throat revealed some blood in the posterior oropharynx. There are a few macular purplish-red lesions on his lips and oral mucosa. There are decreased breath sounds and dullness to percussion in the right base. You can also hear a bruit over the left lateral chest wall. Examination of the heart reveals a regular rhythm with no murmurs, rubs, or gallops. The abdomen and genitalia are normal. There is no cyanosis or edema but clubbing is noted in the fingers of both hands.

Laboratory data reveals normal urinalysis and blood chemistries. CBC shows a
hematocrit of 35%, WBC of 9.3 with a normal differential, and platelet count of 360K. EKG shows a normal sinus rhythm with a rate of 90 beats per minute. Chest radiograph shows a faint density in the left lower lung field.
Case 3

You are called to see a patient in the hospital who has coughed up one cup full of bright red blood. He has been in the hospital for five days and is on IV antibiotics for pneumonia.

He is a 48 year-old white man who was admitted to the hospital when found unconscious on the street. He states that he had fever and chills for 4 weeks. He also complained of a cough that was productive of brownish fetid sputum. He states that he had lost 15 lbs. over the last two weeks and that otherwise his symptoms had been of gradual onset. Currently he feels tired and run down. He has no appetite. He states that he is really short of breath and has dyspnea with walking one city block. He has a vague chest discomfort in his right chest. He denies paroxysmal nocturnal dyspnea, orthopnea, and pedal edema.

Review of systems reveals that he has occasional headaches for which he takes "Goody Powders". He is near-sighted. He has decreased hearing on the right. He has had tooth pain for several months. He complains of nausea and occasional vomiting, and some diarrhea.

Past medical history reveals that he has been admitted to the hospital for delirium tremens two times in the past 3 years. He had pneumonia 2 years ago. He had an appendectomy 10 years ago. He denies allergies. His only regular medication is the "Goody Powders" that also seems to help his tooth ache.

Social history reveals that he is separated and has been unemployed for the last three years. He has smoked 2 packs of cigarettes a day and has for over 30 years. He currently drinks 1/2 pint of whiskey per day when he can get it.

Family history is not recalled.

Physical examination reveals a thin white man with mild respiratory distress. T 101.9, BP 130/70, P 110, R 24. Examination of his mouth shows missing teeth and several carious teeth. His breath odor is fetid. Chest auscultation includes rhonchi on the right. Cardiac examination is normal except for resting tachycardia. Examination of the abdomen reveals a liver span of 15 cm by percussion and a palpable liver edge. The liver is moderately tender. The genital examination reveals small testicles. He has bilateral palmar erythema. The remainder of the exam is unrevealing.
Laboratory data show mild pancytopenia: hematocrit 34 with microcytic, hypochromic indices, WBC 3.7 with 88% neutrophils, 10% bands, and 2% lymphocytes. Blood chemistries include Na = 133, K = 3.4, Cl 89. Urinalysis is normal. The liver enzymes are pending.

Chest radiograph reveals several infiltrates in the right upper lung field and right apex with a 4 cm cavity in the right upper lung zone posteriorly. The radiograph from one day earlier appeared to show the cavity opacified while today's radiograph shows an air fluid level in the cavity.
Case 4

A 30 year-old black woman, an active duty Army SSG, complains of gradually worsening dyspnea over the year prior to arrival. She also notes a cough that began 4 or 5 months ago.

Her MOS is 95B (military police officer) and she rarely has to run or climb stairs while at work. She does find it more difficult to pass the run portion of her APRT and has added 2 minutes to her 2 mile run time. When doing work around the home, she gets short of breath more easily doing her usual tasks. Her cough is productive of scant grey mucus, and but she denies chest discomfort, fevers, chills, sweats, hemoptysis, orthopnea, PND, and pedal edema.

Review of systems is remarkable for painful lumps on the anterior aspect of her lower extremities that she attributes to some kind of allergic response to cocoa butter. She has also noted joint aches in her shoulders, knees and ankles.

Past medical history includes: 1. two pregnancies and two live births (8 years and 6 years ago); 2. tonsillectomy and adenoidectomy as a child.

Social history: She does not smoke tobacco and does not drink alcohol. She lives with her husband and two healthy children

Family history is positive for COPD, uterine cancer and hypertension.

Physical examination reveals a mildly anxious woman who walks briskly to your office. Vital signs include BP 110/70, P 92, R 14, and T 98.4. Pulse oxygen 96% saturated at rest. The head, ears, nose and throat are normal. There is axillary, epitrochlear, and inguinal adenopathy. Lung examination is normal. Heart sounds include a normal SI and S2 without murmurs, rubs or gallops. The abdomen is soft, nontender and without masses or organomegaly. There is no clubbing or cyanosis. There are seven tender, red raised papules on the shins of both legs.

Evaluation of the laboratory data reveals normal urinalysis, blood counts, and blood chemistries except for an elevated calcium level at 10.6 mg/dL. Pulmonary function tests showed a forced vital capacity of 3.42 L (77% of predicted), FEV1 2.83 L (75% of predicted), and FEV1/FVC of 0.83. A chest radiograph is obtained.
Case 1 Consult
You are called to see a 45 y/o female with hyponatremia.
HPI: The patient underwent a total abdominal hysterectomy and bilateral oophorectomy (TAH-BSO) 1 day ago for menorrhagia and pelvic pain secondary to endometriosis/fibroids, complicated by severe anemia. Her pre-surgery was Na = 136 mmole/L and is now = 118 mmole/L. The surgery was uncomplicated and her post-operative course is characterized by persistent nausea and an ileus and is not taking anything by mouth. She is currently receiving morphine for pain delivered by a patient controlled analgesia (PCA) pump and compazine every 6 hours for nausea. Her current intravenous fluid is 5% dextrose and ½ half normal saline (D51/2 NS) at a current rate of 84 ml/hour. This had been reduced from 125 ml/hour after 2 liters had been infused. Total intake/output over the last 24 hours recorded in the chart including both operative and post-operative infusions is 7 liters in and 2.3 liters out with an hourly urine output now ranging from 60-90 ml/hour

Her past medical history is significant for hypertension for 10 years, treated with 25 mg HCTZ daily. Depression for 5 years treated with 20 mg Paroxetine daily. Her outpatient medications were discontinued on the morning of surgery and have not been restarted.

Physical Exam: Patient is noted to be very drowsy, oriented with prompting, and can barely talk with you. Vital Signs: Wt. 70 kg; BP 115/62; P 90; RR 15. Temperature: 98.7 °C, Pain: 4/10.
Aside from rare bowel sounds, a recent abdominal incision, and trace LE edema, physical exam is unremarkable.

Current (within last 3 hours) LABS: Na 118; Cl 79; HCO3 29; K 3.7; Glucose 95; BUN 6; Creatinine 0.8; Ca 8.9; PO4 3.0; TP 7.2; Alb 3.5; LFT’s normal. Hct 36%; WBC 10K; Plt 275K. Serum osmolality 247
Urinalysis: specific gravity 1.010; pH 6.0; large blood; trace protein. TNTC isomorphic RBCs and 5-10 squamous epithelial cells per low powered field. Urine Na: 132 mEq/L; Urine Creatinine: 89 mg/dL; Urine K: 25mEq/L; Urine volume: 300ml; Urine osmolality: 312 mOsm/Kg

Steps in Diagnosis of Hyponatremia -- Basis Questions in the diagnostic approach
•Is it real?
•Is it acute or chronic?
•Is it symptomatic?
•What is the volume status? (This will ultimately dictate treatment.)
•What is/are the likely etiology(ies)?
REMEMBER: In the preliminary work-up of hyponatremia, determine the patient’s volume status and evaluate for the presence of any pharmacological agent that may affect ADH release or action.

Case Questions:
1. Does she have “true” hyponatremia”?
2. How do you know she has true hyponatremia?
3. How would you check this?
4. Is there evidence of pseudo-hyponatremia?
5. How do you check this?
6. Calculations: Osmolal gap:
   - Calculate her FeNa: \( \frac{U_{Na}/P_{na}}{U_{crea}/P_{creat}} \)
   - Calculate her TBW:
   - Calculate her water excess:
   - Calculate her sodium deficit:
7. Is the hyponatremia Acute or Chronic?
8. Is it symptomatic?
9. What is her volume status?
   - Hypervolemic?
   - Hypovolemic?
   - Euvolemic?
10. What are the potential and contributing etiologies (ies) of her hyponatremia?
11. Treatment: Suggest ways of managing her hyponatremia.

Case 2: Inpatient Admission

CC: fatigue, poor exercise tolerance, “balance” problems while standing and walking, and the sensation of being cold all the time.
HPI: 68 y/o white male with moderate-severe congestive heart failure secondary to ASCVD, admitted by his cardiologist for hyponatremia and chronic renal disease (CKD). His last measured ejection fraction was (EF) 20-25% with evidence of moderate diastolic dysfunction. He received an implantable cardioverter-defibrillator (ICD) 2 years ago. He has a greater than 20 year of hypertension, and peripheral vascular disease, but does not have significant anatomical renal artery stenosis, and but does have has high renal resistive indices. According to his cardiologist, his medications are optimized.

MEDS: Lasix 40 mg bid; Carvedilol 25 mg bid; Ramipril 10 mg daily; Hydralazine 25 mg bid; Coumadin 2.5 mg daily; Atorvastatin 40 mg daily. All medications have been taken at these doses for greater than 3 months.

PE: Tired appear white man alert, oriented, and conversant in no acute distress. Vital signs: BP 98/60; P 58; Respirations 18; Wt. 82 kg. Pulmonary: Lungs with fine rales extending from mid-lung fields to the bases bilaterally.
CV: S1 and S2 soft; +S3; + 3/6 systolic regurgitant murmur at apex extending into axillae. + JVD; + hepatojugular reflux; bilateral 3+ pitting edema to the knee.

Abdomen: liver edge 1 cm below right costal margin.

LABS: Na 124; K 4.8; Cl 86; HCO3 32; BUN 33; creat 1.8 mg% (eGFR 35); Glucose 92; AST/ALT 55/72; TP 6.8; Ca 8.8; WBC 3.6; Hct 38%; Plt 249K. Serum osmolality 272 UA: specific gravity 1015; pH 5.0; trace protein; negative blood. SSA negative. Urine Na 55 mEq/L; Urine creatinine 95; Urine K: 60 mEq/L Urine osmolality 510 mOsm/L. Urine output first 24 hours hospital is 500 ml.

Questions:

1. Laboratory and Calculations
   a. Osmolal gap:
   b. Calculate his FeNa: (U_{Na}/P_{Na} / U_{creat}/P_{creat})
   c. Calculate his TBW:
   d. Calculate his water excess:
   e. Calculate his sodium deficit:

2. Is the hyponatremia Acute or Chronic?
3. Is it symptomatic? Yes.
4. What is his volume status?
   a. –Hypervolemic?
   b. –Hypovolemic?
   c. –Euvolemic?

5. What are the potential and contributing etiology (ies) of his hyponatremia and provide a brief description of the mechanism(s)

6. Treatment: Suggest ways of managing his hyponatremia.

I. Objectives

The purpose of this session is to enable the student to gain an understanding of the mechanisms of sodium and water balance in volume regulation. An understanding of how the body normally maintains volume balance is essential in the diagnosis and treatment of alternations in plasma sodium concentration. The history and physical examination information provided in the clinical case presentations will allow the student to apply this knowledge.

This section of the syllabus will emphasize the importance of eliciting key findings in the history (i.e. what patient likely has and what they are at risk for--inductive and deductive reasoning approaches) and physical exam will stress the importance, and means, of determining the patient’s volume status. Key additional laboratory tests that can assist the clinician will also be discussed. Normal physiology and pathophysiology will be used as the framework for understanding the approach to disorders of sodium concentration. A stepwise heuristic will be presented to help you with evaluating the patient with hyponatremia. Finally, this section will also present a schema (or algorithm) to supplement your approach to the diagnosis and treatment of the hyponatremic patient.
More specifically, at the end of this session, students will be able to:

1. List the history and physical examination clues to determine volume status
2. Understand the use of history and physical exam clues as well as serum and urine studies to diagnose common hyponatremia syndromes (to include the causes of and how to diagnose pseudohyponatremia)
3. Classify a patient as having hypovolemic, euvolemic, or hypervolemic hyponatremia and know the common causes of each category.
4. Understand the basic treatment approach to hyponatremia based on volume status— i.e. how to treat hypovolemic, euvolemic, and hypervolemic hyponatremia
5. List the indications for using hypertonic saline in a hyponatremic patient

II. Key Definitions

1. **Hyponatremia/hypernatremia**: disorders of water metabolism, defined respectively as too much and too little total body water.
2. **Hypovolemia/hypervolemia**: disorders of total body sodium.
3. **Dehydration**: rigorously, the state of having too little body water (e.g., hyponatremia). Often use colloquially to mean hypovolemic, but strictly speaking this is not true—one needs to have an elevated serum sodium concentration to fulfill this definition.
4. **Extracellular fluid volume (ECF)**: volume correlated with total body sodium, including intravascular and extravascular components. Determination of ECF establishes hyper- vs. hypo- vs. euvolemia.
5. **Effective circulating volume**: the intravascular blood volume that engages the regulatory systems controlling extracellular fluid volume.

III. Basic Science Highlights

**III.A. Overview**

Total Body Water (TBW) in terms of body weight = 60% male; 50% female (average)

- **Habitus**: 70/60% lean and 50/42% obese
- **Age**: Infant 1st year 77% - Elderly Male 50% - Female 45%
- **Distribution**: 60% ICF -- 40% ECF in terms of body weight

ECF: ¾ Interstitial Fluid; ¼ Plasma; Transcellular
(approximately 0.5 liters)

Figure 1: Refer to Figure by MIT OpenCourseWare | Free Online Course Materials
Remember Total Body Water quantity calculated in this manner is a clinical estimate NOT a specific exact amount. This is important whenever TBW is used in a calculation of water excess or sodium deficit.

The monograph "Body fluid volume regulation in health and disease" by Abraham and Schrier provides an essential concise but comprehensive discussion of the pathophysiology of volume regulation that will not be repeated in this handout.

The key to mastering these topics is to appreciate the difference between regulation of osmolality (which is done by regulation of water intake and excretion) and regulation of circulating volume (which is primarily a matter of sodium intake and excretion). Thus hyponatremia and hypernatremia are primarily an issue of water metabolism and only secondarily an issue of sodium balance. Table 1 provides an overview of the physiology of osmoregulation vs. volume regulation. A second key is to appreciate that arginine vasopressin (AVP, also known as anti-diuretic hormone or ADH) is a primary effector of osmoregulation, but is also a secondary effector of volume regulation. In states of severe depletion of effective circulating volume, ADH will be stimulated even at the expense of decreasing plasma osmolality.

<table>
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<th>Table 1</th>
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<td><strong>What is being sensed</strong></td>
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<td><strong>Sensors</strong></td>
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<td>Hypothalamic osmoreceptors (non-osmotic stimulators of ADH: severe volume depletion, nausea, pain, stress)</td>
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Abnormalities of plasma sodium concentration are common with the incidence of hyponatremia as high as 1.0+% of patients presenting at a hospital emergency room and as high as 5% of hospitalized patients usually resulting from interventions during the hospitalization. With the aging of the population it is of note that older individuals have a higher incidence of hyponatremia because of multiple factors including: a higher incidence of medication usage or diseases that cause or are associated with low concentrations of serum sodium and an apparent enhanced vasopressin response to hyperosmolality.

An understanding of the causes of changes in plasma sodium concentration in combination with a comprehensive patient history and physical provides the basis for appropriately directed diagnostic and therapeutic interventions. To recognize and effectively treat these conditions it is essential to understand the concept of body fluid compartments and physiological mechanisms that control their volume. A clear determination of the patient's volume status is essential in the evaluation of a patient with an abnormal plasma sodium.

The simple measurement of the plasma sodium concentration, the Na⁺: H₂O ratio provides important information as to the presence of sodium loss and/or water gain. Serum electrolyte concentrations often do not reflect total body stores. Low plasma sodium concentration or hyponatremia can, and frequently does, occur despite total body sodium excess (edematous states); hypernatremia, on the other hand, usually results from dehydration (pure water loss) with an associated decrease in total body sodium. By example, the Na⁺: H₂O ratio helps to provide a distinction between salt and water loss and dehydration. Patients with dehydration are always hypernatremic whereas those with salt and water loss typically have a plasma sodium concentration that is normal or reduced.

The kidney is the primary effector for the regulation of body volume through the reabsorption/excretion of salt and water in response to receptor sensed changes in volume status. In brief, 180 L of glomerular filtrate is generated per day with sodium reabsorbed at multiple sites along the nephron and directly linked to the reabsorption of a variety of other cations and anions. Solute free water generation occurs in the ascending limb of Henle (diluting segment) by Na: K: 2Cl reabsorption without water. Antidiuretic hormone (ADH) quantitatively determines the reabsorption of solute free water primarily in the collecting duct with a resultant range of urine osmolality from 50 to 1200 mOsm/kg. ADH also regulates thirst. These normal mechanisms can be disrupted by conditions/drugs that effect receptors, GFR, sodium/potassium handling by the kidney, release of ADH, and/or the renal responsiveness to ADH.

III.B. Hyponatremia

Hyponatremia refers to a low sodium concentration in plasma, not to total body sodium. Hyponatremia reflects a relative excess of water in relation to sodium. It is always due to an alteration in the kidney's ability to excrete ingested or infused water. This is usually due to an inability to normally suppress ADH release in response to a decrease in plasma
tonicity (effective osmolality), and the inability to form appropriately dilute urine. The diluting capability of the human kidney allows for the generation of a minimum urine osmolality of 50 mOsm/kg. As normal subjects excrete 600 to 900 mOsm/kg of solute per day, primarily sodium and potassium salts and urea, the maximum urine output may be 10 to 18 L/day. [900 mOsm/day - 50 mOsm/kg = 18 L]

REMEMBER: Hyponatremia is the most commonly identified electrolyte disorder with multiple potential contributing etiologies and significant clinical consequences. In the preliminary work-up of hyponatremia, determine the patient’s volume status and evaluate for the presence of any pharmacological agent that may affect ADH release or action.

Three laboratory findings provide important information in the differential diagnosis of hyponatremia:

- **Plasma osmolality** - the ratio of plasma solutes, primarily sodium salts, to plasma water. This can be measured directly, or in the absence of significant other solutes can be estimated as a calculated osmolality

  \[ \text{Posms} = 2 \times [\text{Na}] + [\text{glucose (mg/dl)/18}] + [\text{urea (mg/dl)/2.8}] \]

  A measured plasma osmolality 10mOsm greater than predicted is described as an “Osmolal GAP” and identifies the presence of unspecified solutes. Examples of substances and their calculated contribution included: Ethanol (mg/dL)/4.6, Mannitol (mg/dL)/18, and Ethylene Glycol (antifreeze) mg/dL6.2. Presence of a “Gap” requires both a detailed history and a appropriate blood screen for possible ingested toxic substances.

- **Urine osmolality** (reflects water reabsorption and level of concentration activity); and

- **Urine sodium concentration** (reflection of renal response to a perceived volume status with resulting sodium excretion/retention) The fractional excretion of sodium FeNa (The fraction of the filtered sodium that is excreted by the kidney.) is also used to reflect the perceived vascular volume status as demonstrated by renal tubular sodium handling. The kidney normally reabsorbs approximately 99% of the filtered sodium with a baseline fractional excretion of 1%. Higher excretion rates in the absence of diuretics that increase sodium excretion or renal failure reflect a response to perceived “hypervolemia” whereas lower excretion rates (<1%) reflect sodium retention as a response to perceived “hypovolemia”.

III.B.1. Causes of Hyponatremia

(i) Pseudohyponatremia – Normal ADH Levels

In pseudohyponatremia the measured reduced plasma sodium concentration (Na⁺: H₂O ratio) is associated with a plasma osmolality that is normal or elevated. Plasma can be thought of as consisting of two components: plasma water plus water-free protein and fats. The normal water fraction of plasma is 93% with fats and proteins accounting for the remaining 7 percent. Sodium is dissolved in the water component of plasma,
• Normal plasma osmolality - A normal plasma sodium concentration of 142 mEq/L actually represents a concentration in plasma water of 154 mEq/L. The plasma water fraction may fall below 93% with marked hyperproteinemia or hyperlipidemia. In these settings, the plasma water sodium concentration and plasma osmolality are unchanged, but the measured sodium concentration will be reduced because the specimen contains less plasma water.

• High plasma osmolality is most often due to hyperglycemia or the administration and retention of hypertonic mannitol. This causes a shift of water from the interstitial and intracellular spaces into the vascular space. In general, the plasma sodium concentration will fall by 1 mEq/L for every 62 mg/dL (3.5 mmol/L) rise in the plasma concentration of glucose or mannitol.

• Urea, like glucose, contributes to the measured plasma osmolality. Unlike glucose, however, it is not an effective osmole and elevations in urea do not cause shifts in water from the intracellular to extracellular space. Therefore, elevations in serum urea are routinely not a cause of hyponatremia.

(ii) Decreased Effective Arterial volume – Elevated AHD Levels – Decreased Plasma Osmolality

*Effective arterial volume* depletion (hypovolemia) is a potent stimulus to ADH release and can overcome the inhibitory effect of decreased plasma tonicity on ADH secretion. Other terms synonymous for effective arterial volume are effective blood or circulating volume. Thus, hyponatremia can develop in patients any of the following situations.

• True volume depletion: The condition in which extracellular fluid volume is reduced and, when severe, leads to a clinically apparent reduction in tissue perfusion. This includes volume changes resulting from diuretic usage, particularly thiazides. Salt and water loss comes primarily from the extracellular fluid whereas pure water loss (dehydration) comes from the total body water, only about 40 percent of which is extracellular. Thus, for dehydration to produce the same degree of extracellular volume depletion as salt and water loss, 2.5 times as much fluid would have to be lost.

• Congestive heart failure: In CHF, the decreased cardiac output is the primary cause of the decrease in effective arterial volume. The neurohumoral changes include increased-secretion of the three "hypovolemic" hormones - renin, antidiuretic hormone (ADH), and norepinephrine. These limit both sodium and water excretion in an attempt to return the effective volume status to normal. ADH allows distal water reabsorption. Angiotensin II and norepinephrine limit distal water delivery through a decrease in GFR and by an increase in proximal sodium and water reabsorption. Both low cardiac output and high angiotensin II levels are potent stimuli to thirst, leading to enhanced water intake. Remember: Patients with CHF, particularly those with edema are by definition, sodium and water overloaded, thus the decreased effective arterial volume drives the ADH response.

• The severity of the defect in water excretion and the associated level of hyponatremia parallel the severity of the heart disease. Patient survival is significantly reduced when the plasma sodium concentration is below 137 mEq/L.
Cirrhosis: Hyponatremia is a common problem in patients with advanced cirrhosis and ascites. As in CHF the decreased effective arterial volume drives the ADH response and the pathogenesis is directly related to the hemodynamic changes and secondary neurohumoral adaptations that occur in these patients. Cirrhotic patients with ascites commonly demonstrate sodium and water retention, increased total body sodium, and hyponatremia. The degree of hyponatremia and sodium retention parallels the severity of the hepatic disease. Patient survival is significantly reduced when the plasma sodium concentration is below 130 mEq/L.

For both congestive heart failure and cirrhosis plasma sodium concentrations below 125 mEq/L often indicates extremely severe organ failure.

A patient with the nephrotic syndrome can also present with hyponatremia based on a decrease in effective arterial volume although not as common as for CHF and cirrhosis the underlying mechanism is the same.

(iii) Primary Water Gain: Elevated ADH Levels – Decreased Plasma Osmolality
Syndrome of inappropriate ADH secretion [SIADH] - Persistent ADH release and water retention is seen in a variety of disorders/situations that are not associated with hypovolemia. A non-exhaustive list includes: ADH release from the pituitary due to certain CNS lesions, various pulmonary lesions, endocrine disorders, excessive pain, and drug induced release (morphine, clofibrate, tricyclics, antineoplastic agents); ADH release from other sources including solid neoplasms, and granulomatous diseases; and drugs that enhance ADH activity by increasing cAMP levels in the collecting duct (chlorpropamide, prostaglandin synthesis inhibitors).

Hyponatremia in SIADH is essentially due to a combination of primary water retention and secondary solute (sodium - potassium) loss. The primary event is the ADH-induced water retention resulting in volume expansion that activates secondary natriuretic mechanisms to restore near normal volume (euvolemia). In SIADH, volume regulation is intact and thus the administration of excess sodium will be accompanied by rapid excretion in the urine. Severe hyponatremia may be associated with potassium loss and the loss of osmotically active potassium contributes to the reductions in the plasma osmolality and sodium concentration. Treatment is based on resolving the underlying condition (if possible) and the institution of water restriction in appropriate cases.

Reset Osmostat: Accounts for between 25 and 30 percent of SIADH cases regardless of cause. Identification of a reset osmostat with stable mild hyponatremia (usually between 125 and 135 mEq/L) is important, as this usually does not require a therapeutic intervention. Since osmoreceptor function is normal around the new baseline, attempting to raise the plasma sodium concentration will only increase ADH levels and thirst as seen with water restriction in normal subjects. The diagnosis can be confirmed clinically by observing the response to a water load, 10 to 15 mL/kg given orally or intravenously.

(iv) Disorders In Which ADH Levels May Be Appropriately Suppressed
Advanced renal failure - Relatively normal water excretion is preserved with mild to moderate renal failure. In the presence of advanced renal failure the minimum
urine osmolality rises to as high as 200 to 250 mOsm/kg due to an osmotic diuresis in the remaining functioning nephrons despite the appropriate suppression of ADH. This results in an inability to excrete an appropriately dilute urine.

- Primary polydipsia - Primary polydipsia is due to a primary stimulation of thirst. It is most often seen in anxious, middle-aged women, in patients with psychiatric illnesses, and with hypothalamic lesions that directly affect the thirst centers. The plasma sodium concentration is usually normal or only slightly reduced since the excess water is readily excreted. If water intake exceeds 10 to 15 L/day potentially fatal hyponatremia may ensue even though the urine is maximally dilute with an osmolality below 100 mOsm/kg. Symptomatic hyponatremia can also be induced with an acute 3 to 4 liter water load, particularly if there is also an impairment in water excretion, such as seen with induced ADH release or concurrent diuretic therapy.

IV. Basic Approach to Diagnosis

IV.A. Clinical Presentation

The symptoms directly attributable to hyponatremia are related both to the severity and in particular to the rapidity of onset of the change in the plasma sodium concentration and reflect neurologic dysfunction induced by cerebral edema. Nausea and malaise are the earliest findings, and may be seen when the plasma sodium concentration falls below 125 to 130 mEq/L. This may be followed by headache, lethargy, delirium, and obtundation and eventually seizures, coma and respiratory arrest if the plasma sodium concentration falls below 115 to 120 mEq/L.

The degree of cerebral edema is less with chronic hyponatremia as osmolyte adaptation normally begins within 24 hours of the onset of hyponatremia. This adaptation can be so efficient that it is not uncommon to see patients with heart failure or the syndrome of inappropriate ADH secretion (SIADH) who are asymptomatic despite a plasma sodium concentration that is persistently between 115 and 120 mEq/L. When symptoms do occur in chronic hyponatremia, the plasma sodium concentration is generally below 110 mEq/L and there has usually been an acute exacerbation of the hyponatremia.

IV.B. Diagnostic Algorithm

A schematic for the approach to diagnosis is given in Figure 2. There are three keys to diagnosis. The most important is establishing extracellular volume status. (A diagnostic approach to ECF volume status is summarized in Table 2.) Next, it is important to assess overall plasma hypotonicity, as isotonic or hypertonic plasma would indicate pseudohyponatremia or the presence of other active osmolar agents. Finally, it must be determined whether there is physiological evidence of ADH activity. If ADH is shut off, then the urine will be maximally dilute (< 100 mOsm/kg), indicating excess water intake. If ADH is active, determination of the effective circulating volume will indicate whether it is normal (in case of volume depletion or edematous disorders), or abnormal (in the cases of euvolementa). In cases of hyper- or hypovolemia, the urinary sodium concentration will aid in determining if the disorder is due to a renal tubular
mechanism (in case of $U_{Na} > 20$ mEq/L) or from a process outside the renal tubules ($U_{Na} < 10$ mEq/L, or a fractional excretion of $< 1\%$).

**Figure 2**

![Diagram of osmolality and volume assessment]


The biggest diagnostic challenge is the patient with hypotonic hyponatremia and euvolemia. Next to volume status, the most important part of the history and physical examination is an exhaustive review of medications. Table 2 lists drugs commonly associated with hyponatremia along the mechanism, if known. In some diagnostic schemes, drug-induced hyponatremia is listed among the causes of SIADH, however it is best to consider it a separate category.
Table 2

Because the syndrome of inappropriate ADH release (SIADH) (inappropriate for volume status) is common in hyponatremic hospitalized patients, clinicians often initially jump to this diagnosis, but in fact this is a diagnosis of exclusion. It should be the last thing you consider, not the first. Table 3 lists the criteria, which must be satisfied after other causes are ruled out.

Table 3

Table 4 is a relatively comprehensive listing of causes of SIADH. Notice that most etiologies can be divided into the broad categories of carcinoma-related, pulmonary disease, and CNS disorders.

Table 4

V. Treatment: Remember these are only suggestions, review each patient completely and obtain appropriate clinical and laboratory data.

Hyponatremia can only be managed safely after first determining the cause. Empiric water restriction or sodium loading is dangerous. The optimal rate of correction varies with the clinical state of the patient. Most patients with hyponatremia are asymptomatic and have a plasma sodium concentration above 120 mEq/L. Treatment typically consists of the administration of: a) isotonic saline or oral NaCl if the patient has true volume depletion or b) water restriction in the syndrome of inappropriate ADH secretion or edematous states, such as heart failure or hepatic cirrhosis. In comparison, more aggressive therapy including consideration of hypertonic saline infusion is indicated in those patients who have symptomatic or severe hyponatremia (plasma sodium concentration below 110 to 115 mEq/L). It is important to appreciate that potassium is as osmotically active as sodium and that giving potassium can raise the plasma sodium concentration and osmolality in a hyponatremic subject. The net effect is that concurrent administration of potassium must be taken into account when calculating the sodium deficit.

Overly rapid correction may be deleterious, especially in patients with chronic asymptomatic hyponatremia. Such a correction can lead to an osmotic demyelination
syndrome that is associated with the delayed onset (2-6 days) of potentially severe neurologic symptoms that may be irreversible. Premenopausal women seem to make a less efficient osmotic adaptation to hyponatremia and as a result, they appear to be at greater risk for severe hyponatremic symptoms. They are at much greater risk (up to 25-fold when compared to men) for residual neurologic injury following symptomatic hyponatremia and may be at a higher risk for treatment-associated complications.

A suggested algorithm for the treatment of hyponatremia is shown in Figure 3 with an alternative approach for symptomatic patients provided below from a Consensus Conference on Exercise Induced Hyponatremia. Both methods call for caution in the rate at which the serum sodium is corrected.

Figure 3

Correction Rate for Hyponatremia
In all symptomatic patients (i.e., seizures, coma) with hyponatremia regardless or duration:
Consensus Conference for Exercise-Associated Hyponatremia (Clin J. Sports Med. 2005) recommended 100 ml bolus infusion of 3% NaCl, repeated up to 2X at 10 minute intervals until clinical improvement. (Approx. 5-6 meq/L increase in a 50 Kg woman).

In chronic hyponatremia, correct at a rate not more than 0.5 meq/L/Hr for first 4 hours, and < 10 meq/L in first 24 hours, < 18 meq/L in first 48 hours, < 20 meq/L in first 72 hours.
Patients at high risk for osmotic demyelination (alcoholics, malnourished, patients with liver disease) may require slower correction!

V. Summary and Consequences of “Mild” Hyponatremia
Hyponatremia is a commonly seen and important disorder of water metabolism, and its evaluation requires a clear understanding of the differences between osmoregulation and volume regulation. The diagnostic algorithm is based on a) assessment of extracellular fluid volume and effective circulating volume, and b) determination of urinary dilution function. Treatment depends upon the underlying cause, with the most important factor being the avoidance of over-rapid correction. The short and long term consequences of this extremely common electrolyte disorder are summarized below in representative papers from the current literature.

Clinical questions:
Is it reasonable to set a clinical goal of a serum sodium > 125?
Is mild hyponatremia without morbidity?
• 16 patients: mean [Na+] 128±3 mEq/L “Clinically asymptomatic”
• Attention defects demonstrated for tests of visual and auditory stimuli – abnormal response with increased latency
• Unstable in Rhomberg position and marked problem in tandem walk.
• Demonstrated increased risk of falls

The American Journal of Medicine (2009) 122, 857-865 **Hyponatremia and Mortality**

Prospective cohort study of 98,411 adults. Main outcome measures:
In-hospital, 1-year, and 5-year mortality.
Outcomes in patients with varying degrees of hyponatremia vs. patients normal serum sodium concentration.

**Results:** Hyponatremia (serum sodium concentration >135 mEq/L) 14.5% of patients on initial measurement.

• Compared with patients with normonatremia (135-144 mEq/L), older (67.0 vs. 63.1 years, \( P \) .001) more comorbid conditions
• In multivariable-adjusted models, patients with hyponatremia had an increased risk of death in-hospital, at 1 year, and at 5 years.
• Increased risk of death evident with mild hyponatremia (130-134 mEq/L)
• Relationship between hyponatremia and mortality was specifically pronounced inpatients with cardiovascular disease, metastatic cancer, and admitted for procedures related to the musculoskeletal system.
• Resolution of hyponatremia during hospitalization attenuated the increased mortality risk.

Back to our patients…

Case 1

1. Does she have “true” hyponatremia”?  Apparently yes.
   a. What is normal serum osmolality?  275-290 mOsm/Kg
2. How do you know she has true hyponatremia?
   a. No apparent **unmeasured osmols** (glucose and BUN are normal. Not receiving mannitol. Not using EtOH. Glycine or sorbitol should be gone by now if used during surgery).
3. How would you check this?
   a. Send serum osmolality (get a urine osmolality & sodium and creatinine) and check against the calculated osmolality.
   b. The serum osmolality is 247 mOsm.
   c. Calculated serum osmolality = 2(Na) + (BUN mg/dl/2.8) + (Glucose mg/dl/18) = 236 + 2 + 5 = 243 mOsm. If the difference is less than 10, there are no significant unmeasured osmols*
4. Is there evidence of pseudohyponatremia?  No
   a. TP and albumin are normal. High protein (post albumin infusion or in setting of paraproteinemia) can increase the volume of the total plasma volume, while the volume of plasma water is unchanged, falsely suggesting a low sodium concentration, eg:150.5 mM sodium in 930 ml plasma water + 70 ml of protein vs. 150.5 mM of sodium in 890 ml
plasma water + 110 ml of protein. 140 mEq Na (nl) vs. 134 mEq Na (psuedohyponatremia).

5. How do you check this? Check the plasma osmolality. This is a function of the aqueous part of plasma only (it is measured by freezing point depression).
   a. There will be a negative discrepancy between the calculated osmolality and the measured osmolality, i.e.: the calculated osmolality will be lower than the true (measured) osmolality.

Laboratory and Calculations
6. Urine osmolality: 312 mOsm/Kg
7. Urine Na: 132 mEq/L; Urine Creatinine: 89 mg/dL; Urine K: 25mEq/L; Urine volume: 300ml
   a. No osmolal gap: 247 – 243 = 4
   b. Calculate her FeNa: 1% (UNa/Pna / Ucreat/Pcreat)
   c. Calculate her TBW: 0.5(70 kg) = 35 L
   d. Calculate her water excess: TBW (based on presenting weight)x (current sodium) = TBW x (desired sodium) The calculated difference in weight account for the water excess.
      i. 35L(118 mEq/L) = x (140 mEq/L) x = TBW
         x = 29.5 L; 35L - 29.5L = 5.5 L
   e. Calculate her sodium deficit: Sodium deficit = TBW (based on presenting weight) x (desired serum Na - actual serum Na)
      i. 35L(118 mEq/L) + ? mEq = 35L(140 mEq/L) ? = 770 mEq

Mass Balance Method

Water excess and sodium deficit calculations are simply clinical guides to give you an idea of the degree of dilution that has occurred with regard to the “normal” total body water. As stated, based on the accuracy of the TBW calculation these data should be used to provide a general guide to the amount of water retention that has occurred.

Next Questions:
8. Acute or Chronic? Acute. It occurred in 1-3 days.
9. Is it symptomatic? Yes. She has depressed mental status and delirium, although narcotics also could be contributing.
10. What is her volume status?
   a. --Hypervolemic?
   b. --Hypovolemic?
   c. --Euvolemic?
   d. It is important to remember that with few exceptions, hyponatremia develops in the setting of continued ADH activity (physiologic or pathophysiologic) despite low osmolality. The inability to excrete excess water leads to hyponatremia.
11. What is the etiology of her euvolemic hyponatremia
Medication reconciliation prior to her surgery may have help to prevent the medication related contributions to her hyponatremia. un-intended outcome.

Use of a thiazide diuretic (prevents maximal dilution – diminished Na⁺ reabsorption in distal convoluted tubule)).
Use of an SSRI (associated with SIADH)
Pain
Narcotic analgesic
Nausea (although this may be a symptom)
Use of hypotonic fluids
? Use of sorbitol or glycine during gynecologic surgery with resultant water load (unlikely in this case but know it for the boards).
Menstruating females are more susceptible.
12. Based on etiologies:
   a. Stop hypotonic IV fluids
   b. Water restriction
   c. Stop diuretic
   d. Time with resolution of pain and nausea will contribute to recovery.
   e. If symptoms persist or worsen could use hypertonic saline infusion: doubtfully necessary in this case.

Case 2

Questions:
Laboratory and calculations
1. Osmolal gap: 272-265= 7 mOsm no “Gap”
2. What is his FENa? 0.7% (sodium retention)
3. Calculate his total body water (TBW) 86kg x 0.6 = 49.2L
4. Calculate his water excess? TBW (based on presenting weight) x (current sodium) = TBW x (desired sodium) The calculated difference in weight account for the water excess.
   a. 49.2L(124 mEq/L) = x(140 mEq/L); x = 43.5 L; water excess≈ 6L
5. Calculate his sodium deficit:
   a. Sodium deficit = TBW (based on presenting weight) x (desired serum Na - actual serum Na) or through the Mass Balance Method

49.2L(124 mEq/L) + ? mEq = 49.2L(140 mEq/L) ? = 787 mEq
787 is estimated total body sodium deficit

6. Is the hyponatremia acute or chronic: CHRONIC
7. Is he symptomatic: Yes although the fatigue may be secondary to the CHF it may also be due to the hyponatremia, also his problem with balance may be secondary to the hyponatremia.
8. What is his volume status? Clinically appears hypervolemic: Edema with Na and H₂O excess
9. What is the pathophysiology of his hyponatremia?
   a. Congestive heart failure with resultant diminished renal perfusion and a
time decreased “effective arterial volume” stimulates ADH production despite
hyponatremia.
   b. Hypothyroidism – may be contributing to the severity of his CHF and may
also effect kidney diluting capacity and ADH responsivity

10. Treatment: Suggest ways of managing his hyponatremia.
   a. 800 ml water restriction; 2 gm Na restriction; increase in diuretic dose or
   All inhibition basically it is to more successfully treat the congestive heart
   failure.
   b. Tolvaptan: ADH receptor blocker.
   c. Thyroid hormone replacement

Practice questions (and answers):
1. Which of the following causes of hyponatremia would be expected to present with
   normal volume status by physical exam?
   a. Nephrotic syndrome
   b. Congestive heart failure
   c. Lung tumor with SIADH
   d. Gastrointestinal bleeding

2. ADH release is directly influenced by all of the following except:
   a. Effective arterial volume
   b. Stress & Pain
   c. Plasma hemoglobin and hematocrit
   d. Serum osmolality

3. Hyponatremia/hypernatremia are best defined as:
   a. disorders of sodium metabolism
   b. disorders of water metabolism
   c. disorders of volume regulation
   d. disorders of renal function

4. What substance does not contribute to the clinical calculation of plasma osmolality?
   a. Plasma glucose
   b. Plasma Sodium
   c. Plasma Protein
   d. Plasma blood urea nitrogen

Answers:
1. C. By definition SIADH presents with normal volume status by physical exam.
   B and c would present with volume overload (edema in both, S3 in CHF) and d
   would be expected to present with volume depletion on exam (orthostasis,
decreased axillary sweat and dry mucous membranes).

2. C. The levels of plasma hemoglobin and hematocrit although may be influenced
   by ADH release and water retention do not themselves affect ADH release. Stress
   and pain cause non-volume and non-osmolality stimulus for ADH release.
3. B. The dysnatremias are disorders of water metabolism as dictated by ADH release and action at the kidney. Sodium metabolism directly relates to volume regulation but hyponatremia can exist with a normal volume and the serum sodium concentration does not necessarily reflect total body sodium content.

4. D. The formula for the clinical calculation of plasma osmolality is:

\[ \text{Posms} = 2 \times [\text{Na}] + \left[ \frac{\text{glucose (mg/dl)}}{18} \right] + \left[ \frac{\text{urea (mg/dl)}}{2.8} \right] \]
Small Group Discussion Model: Hyponatremia Case Studies

In the small group session, a preceptor facilitates a discussion of key clinical aspects during the session. The goals of the small group exercise are for the participants to develop clinical reasoning skills as the fundamental building blocks of clinical medicine and be able to discuss the basis for their conclusions in a peer environment. These goals are achieved via the following objectives independent of the content specific objectives:

1) Illustrate major diagnostic entities (common and/or serious) for the topic.
2) Describe typical patterns of presentation for these diagnostic entities (classic or typical patterns)
3) Construct prioritized problem lists
4) Create a relevant differential diagnosis
5) Demonstrate clinical reasoning by justifying the differential diagnosis using key clinical information or decision points towards establishing the diagnosis
6) Reinforce use of proper medical terminology and pathophysiology germane to each case

Hyponatremia Case Study 1

A 69 year old retired Major General presents to the emergency room with progressive dyspnea on exertion, new ankle swelling and unintentional weight gain. He has awakened from sleep due to his dyspnea several times over the past week has slept in a chair for the last 3 days. He has a history of hypertension and a recent lateral wall myocardial infarction. He has not been complying with his low sodium diet and his only medications are ECASA and atenolol. He has also noticed an increased perception of thirst.
Vitals: BP=108/60, HR=96 with no orthostatic changes
Neck veins are distended to 14cm at a 45-degree elevation
Heart: RRR. Normal S1 and S2. + S3 and S4
Lungs: Rales at bases bilaterally
Abdomen: NABS. S/NT/ND. No HSM or masses.
Extremities: 2+ pitting edema to knees bilaterally

Lab. Values:
Na=128 mEq/L
K=4.0 mEq/L
Cl=90mEq/L
CO2=30mEq/L
BUN=90mg/dL
Cr=2.2 mg/dL
Glucose=110 mg/dL
BNP=elevated
Albumin=4.0 gm/dL
Serum osmolality (measured)=295 mOsm/kg

Urine
Na=10mEq/L
K=40mEq/L
Osm=780 mOsm/kg
protein=Trace

8:19
1. Create a problem list for this patient’s presentation.

2. What is this patient’s volume status (hypervolemic, euvolemic, or hypovolemic)?
   What history, physical and laboratory clues support your assessment?

3. What are the criteria for orthostatic blood pressure changes? How does this help you in determining a patient’s volume status?

4. What is the differential diagnosis for this patient’s hyponatremia? What is your leading diagnosis?

5. If you assume a diagnosis of congestive heart failure (CHF) with low cardiac output, what is the status of the hormones renin and ADH? Why do you think this is the case? What is the influence of these hormones on a) renal blood flow, b) urine osmolality, and c) urine sodium concentration?

6. What is the mechanism of his increased thirst?

7. Why is the osmolality in the normal range? How does the fact that the osmolality is normal contribute to the mechanism for hyponatremia? What do the urinary osmolality and electrolytes at this point tell you about the activity of the major hormones for volume and osmolarity regulation?

8. Suppose the labs had instead shown a BUN/Cr 23/1.3 and glucose of 720. How would that change your answers to question 7?

   The patient receives a loop diuretic (furosemide) 20mg IV which results in marked improvement in his dyspnea and prompt diuresis. He is sent home with the recommendation to follow a low Na diet and to take furosemide 40mg by mouth (po) daily and lisinopril (ACE inhibitor) 10mg po daily. His shortness of breath and edema resolve over the next couple of days. On re-examination three weeks later, his BP=120/60 and his heart rate is 84.
   Heart: RRR with no murmurs, rubs or gallops
   Lungs: Clear to auscultation and percussion bilaterally.
   Abdomen: NABS. S/NT/ND. No hepato-spenomegaly or masses.
   Extremities: no edema

   Laboratories:
   Na=138 mEq/L
   K= 5.2 mEq/L
   Cl=103 mEq/L
   CO2=26 mEq/L
   BUN=25 mg/dL
   Cr=1.5 mg/dL
   Urine
   Na=40mEq/L
   K=25 mEq/L
   Osm=450 mOsm/kg

9. What is the patient’s volume status now? Why do you think that his plasma sodium level has returned to normal? How do you interpret his new set of laboratory values?
Hyponatremia Case Study 2

An 80-year-old retired Chief Master Sergeant presents to the emergency room with a several day history of progressive confusion and fatigue. He has a history of hypertension, for which he takes hydrochlorothiazide, and tobacco abuse (80 pack/year). He has also been taking an over the counter cough medicine for his chronic cough. Additionally, he complains of a decreased appetite over the past two months with unintentional weight loss (10 lb). He states that he has been frequently drinking water as well as Chinese green tea. He reports no nausea or vomiting but has had some mild constipation as well as a new frontal headache.

On physical examination, he is a well-developed male who appears his stated age. He appears lethargic.
BP=90/56, HR=106 seated; complains of some lightheadedness when standing
HEENT: dry mucous membranes
Heart: RRR with no murmurs or gallops
Lungs: Expiratory wheezing is heard over the right middle lobe
Abdomen: NABS. Soft, nontender, and nondistended. No hepatosplenomegaly, masses or bruits.
Extremities: Clubbing present. No edema
Neurologic: Oriented to person. Unable to do serial “7s” or spell world backwards, 0/3 recall. Strength 5/5 in upper and lower extremities. Sensation intact to light touch, pin prick, and vibration. DTRs 2+ and symmetric.

Laboratory Data:
Na=114 mEq/L
K= 3.5 mEq/L
Cl=78 mEq/L
CO2=26 mEq/L
BUN=15 mg/dL
Cr=1.2 mg/dL
Glucose=100 mg/dL

Urine
Na=60 mEq/L
K=25 mEq/L
Osm=650 mOsm/kg

1. Construct a problem list for this patient’s presentation

2. What is this patient’s volume status? What history, physical and laboratory clues support your assessment?

3. Is this patient’s hyponatremia acute or chronic? What history, physical and laboratory clues support your assessment?

4. List the differential diagnosis for this patient’s hyponatremia. What is your leading diagnosis?

5. List underlying causes for your diagnosis and explain the physiologic mechanisms?
6. How would you treat this patient? Additionally, outline a basic treatment approach to hypovolemic, euvoletic and hypervolemic hyponatremia.

The patient receives therapy resulting in a serum sodium of 128 mEq/L over the next couple of hours and resolution of his symptoms. The patient then receives Tolvaptan (a vaptan). His serum sodium increases to 135mEq/L in the next two hours.

7. What life threatening complication can occur with rapid correction of serum sodium in the setting of hyponatremia?

8. What is the mechanism of action of the vaptans? What is their potential role in the treatment of specific hyponatremic disorders? In what clinical conditions should they not be used?
A 58 year old white man presents to the Intermediate Care Clinic with a three day history of the acute onset of nausea, vomiting, fatigue, cramping, and an unsteady feeling upon rising to an upright position. He has a ten year history of Type II diabetes on oral medication, three years of benign prostatic hypertrophy with obstructive symptoms, a five year history of hypertension, and recently noted proteinuria. Within the last 24 hours he has developed a mild headache that has not been responsive to ibuprofen. He has only been able to drink water or ginger ale and has noted a decrease in his urine volume. He had been doing well prior to this event and had been seen in the Internal Medicine clinic one week prior to the onset of his symptoms and in the Urology clinic one month ago.

Questions:
1. What features of the patient’s history are of particular importance?
2. What are the possible causes of the patient’s symptoms?
3. What is the likely role of the kidney in this situation?
4. What further diagnostic steps and treatments are in order?

You are taking care of a 23 year-old male who is a multi-trauma patient in the ICU. His serum creatinine has steadily risen from 0.9 mg/dL on admission to 7.2 mg/dL over the past week. He has been requiring frequent trips to the operating room for revisional surgery and washouts on his wounds, and has maintained persistent low-grade fevers.

Questions:
1. What are possible contributing factors to his kidney injury?
2. What diagnostic studies may be helpful?
3. What therapeutic steps are indicated?

Objectives:
At the end of this session, students will be able to:
1. Estimate creatinine clearance using the Cockcroft-Gault equation and understand how other estimation equations are used to calculate estimate glomerular filtration rate.
2. Recognize the clinical and laboratory features of the uremic syndrome.
3. Distinguish features of acute versus chronic versus acute-on-chronic kidney failure.
4. Understand the use of bedside history, physical exam findings, and laboratory tests to classify the presentation of renal failure as pre-renal, intra-renal, or post-renal. Examples of urine tests include urine specific gravity, FeNa, urine sodium; urine sediment: red blood cell casts (glomerulonephritis); white blood cell casts (interstitial nephritis); positive urine dipstick for blood without significant red blood cells (rhabdomyolysis); muddy brown casts (acute tubular necrosis).
5. List the indications for urgent dialysis treatment (severe hyperkalemia; uremic symptoms; pericarditis; unmanageable volume overload/pulmonary edema; unmanageable acidosis).
6. Understand the steps for excluding post-renal failure in a patient presenting with acute renal failure (i.e. rule out bladder outlet obstruction with post void residual; rule out ureteral obstruction with renal ultrasound).

7. List the common causes of End Stage Renal Disease (ESRD) in the United States.

8. Understand the natural history of diabetic nephropathy.

9. Name common medications which may contribute to the pathogenesis of kidney failure.

I. Key Definitions

1. **Acute kidney injury (AKI):** disease causing loss of renal function over hours-to-weeks. Also known by older term *acute renal failure.*
   - **Oliguria:** urine volume less than 400-500 mL/day. Associated with more severe forms of AKI.
   - **Prerenal azotemia:** acute decrease in glomerular filtration rate due to renal hypoperfusion in the absence of cellular damage
   - **Acute tubular necrosis:** acute decrease in renal function due to ischemic or toxic cellular damage. It is one of the most common mechanisms of AKI seen in the clinical setting, and because of this, the terms AKI/ARF and ATN are often used interchangeably outside of internal medicine, but this is not always accurate.
   - **Postrenal failure:** decrease in renal function due to an obstructive process involving the tubules, ureters, or bladder.

2. **Chronic kidney disease (CKD):** disease causing loss of renal function over months-to-years.

3. **Diabetic nephropathy:** leading cause of CKD and end-stage renal disease in the Western world.

4. **Uremia:** multi-organ symptom complex resulting from biochemical abnormalities of renal failure

II. Basic Science Highlights

**II.1. Assessment of Renal Function**

The gold standard for assessment of renal function is the *glomerular filtration rate (GFR).* This is not routinely measured because it requires administration of an exogenous substance (e.g., inulin or iothalamate) which is freely filtered and neither secreted nor reabsorbed in the tubules. Instead, the *serum creatinine clearance (CrCl)* is used to approximate GFR. Creatinine is produced at a relatively constant rate in muscles, which is reflected by a stable plasma concentration and urinary excretion:

\[
GFR \approx \text{CrCl} = \frac{(uCr \times V_{\text{Urine}})}{sCr}
\]

- **CrCl = mL/min**
- **uCr = urinary creatinine concentration in mg/dL**
- **V_{\text{Urine}} = urine production rate in mL/min**
- (thus \(uCr \times V_{\text{Urine}} = \text{total mg of creatinine excreted/24 hrs}\)
sCr = serum creatinine concentration in mg/dL

The urine obtained for a creatinine clearance is usually collected over an 8-to-24-hour period, as collections over shorter periods of time are more susceptible to error. The value obtained from the creatinine clearance is not an exact measure of GFR because creatinine is not only filtered but also secreted by the tubules in man. Thus the amount of urine creatinine collected contains a significant amount of secreted (10-20%) as well as filtered creatinine. This is fortuitously balanced out by the fact that the plasma assay for creatinine is also erroneously high by as much as 20% due to the presence of interfering substances.

Ideally, the CrCl is normalized to a body surface area (BSA) of 1.73 m², which is an accepted average adult surface area. Normal values for CrCl are 95 ± 20 mL/min/1.73 m² in women and 120 ± 25 mL/min/1.73 m² in men.

Obtaining a 24-hour urine collection is a cumbersome process. In order to facilitate greater use of CrCl in clinical practice, several formulas have been developed to estimate it just from demographic data and easily obtained lab blood values. Weight, age, and gender influence the body muscle mass, which determines the endogenous creatinine production rate. The following formula designed by Cockroft and Gault in 1976 has traditionally been the most widely-used estimate of CrCl from steady-state serum creatinine levels:

Males: \[ \text{CrCl (mL/min)} = \frac{(140 – \text{age}) \times \text{weight}}{\text{sCr} \times 72} \]
Females: \[ \text{value for males} \times 0.85 \]

sCr = serum creatinine in mg/dL
Age = years
Weight = lean body weight in kg

Note that the Cockroft-Gault equation is not normalized to BSA. This equation gives insight into several important concepts:

1. CrCl is roughly inversely proportional to sCr.
2. A rise in sCr from 1.0 to 1.4 represents a greater loss in renal function than a rise from 1.4 to 2.0.
3. Consider a 40-year old, 72 kg individual. In a male, a normal CrCl (100 mL/min) corresponds to a sCr = 1 mg/dL. In a female, CrCl = 100 mL/min corresponds to a sCr = 0.85 mg/dL. This is reflective of the lower percentage of muscle weight in women.
4. A sCr of 1.4 in a 20-year old 100-kg muscular male athlete represents normal renal function (119 mL/min), while the same value in a 70-year old, 50-kg woman indicates significant impairment (29 mL/min).

Newer equations than Cockroft-Gault more accurately determine estimated GFR (eGFR) from serum creatinine and do not require knowing weight. Thus renal function can be
directly reported in the electronic health record. It is now standard-of-care that an eGFR be given along with serum creatinine in laboratory reports. The Modification of Diet in Renal Disease (MDRD) Study equation (1999) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009) are most frequently used. The calculations are less straightforward than Cockroft-Gault but can be easily automated. The values from these equations are normalized to 1.73 m² body surface area. The MDRD equation is given as an example below; you are not expected to memorize it. Note the correction factor for African-Americans, which should be explicitly reported on the lab results.

\[
eGFR \text{ (mL/min/1.73 m}^2\text{)} = 186 \times (sCr)^{-1.154} \times (Age)^{0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})
\]

GFR and Age: As noted, the age of the patient is factored into the GFR calculations. The reduction in muscle mass that routinely accompanies aging decreases the creatinine pool and thus creatinine production and amount available for filtration. This lowers estimated GFR. The decline in calculated filtration is multifactorial and there is some debate as to whether the extent of decline is based on co-morbid conditions and not necessarily a direct result of the aging process itself. In the evaluation of a patient with decreased GFR, age as a primary cause should be considered to be a diagnosis of exclusion.

eGFR and steady-state sCr: it must be emphasized that the Cockroft-Gault and eGFR estimates are only valid when the serum creatinine is stable (i.e., in steady-state). These equations cannot be used when a patient is having an acute increase or decrease in GFR. Figure 1 illustrates this point: On day 1 there is an instantaneous decrease in the true GFR from 120 to 60. However, the serum creatinine concentration, dependent on both the rate of production and the rate of excretion, rises only gradually. Between days 1 and 3, eGFR based on the serum levels will overestimate true GFR. It is not until day 3, when steady-state is again reached, that eGFR is accurate.

**II.2. Determinants of GFR**

From a simplified physiological standpoint, GFR can be thought of as being determined by three factors:

\[
GFR \sim K_f (P_{GC} - P_{BS})
\]

where \(K_f\), the ultrafiltration coefficient, is a measure of the permeability of the glomerular capillary wall, \(P_{GC}\) is the glomerular hydraulic pressure, and \(P_{BS}\) hydraulic pressure in Bowman’s space. Expanding on this simplification, it is useful to think about decreases in GFR as attributed to either a) a decrease in perfusion pressure (prerenal failure), b) an increase in tubular backpressure (postrenal failure), or c) a loss in the intrinsic filtration area or permeability of the capillary wall (intrinsic failure). This
categorization is a useful diagnostic approach to changes in GFR. (It must be emphasized that real pathophysiology does not cleanly follow these simple concepts, especially in chronic conditions.) You will also remember from physiology that $P_{GC}$ is determined by renal blood flow and afferent ($R_A$) and efferent ($R_E$) arteriole resistances. Table 1 outlines how alterations in the physiological determinates affect GFR.
II.3. Manifestations of Renal Failure/Indications for Dialysis

1. Uremia: a multi-organ symptom complex due to the biochemical abnormalities resulting from renal failure. Uremia is not caused by any single toxin, but is believed to be due to a combination of nitrogenous organic wastes. Blood urea nitrogen (BUN) is commonly used as a marker of the degree of uremia, but urea itself does not cause uremia. The symptoms and signs of uremia (primarily the first four categories listed below) may be indications to start dialysis
   a. Constitutional: anorexia, weight loss, weakness, functional state of malnutrition, hypothermia

<table>
<thead>
<tr>
<th>Physiological Alteration</th>
<th>Determinant Affected</th>
<th>Effect on GFR</th>
<th>Clinical Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased GCW thickness or decrease in capillary surface area</td>
<td>Kf decreased</td>
<td>↓</td>
<td>Hypertension, Diabetes, glomerulonephritis, Advanced CKD</td>
</tr>
<tr>
<td>Decreased RA</td>
<td>Pg increased</td>
<td>↑</td>
<td>Nitrous oxide hyperactivity (early diabetes, protein loading)</td>
</tr>
<tr>
<td>1. Decreased RE</td>
<td>Pg decreased</td>
<td>↓</td>
<td>1. Ang-II inhibition</td>
</tr>
<tr>
<td>2. Increased RA</td>
<td>Pg decreased</td>
<td>↓</td>
<td>2. Vasopressor therapy</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>Pb increased</td>
<td>↓</td>
<td>Kidney stone, prostate enlargement</td>
</tr>
</tbody>
</table>

Table 1
b. Central nervous system: neuromuscular irritability, twitching, convulsions; peripheral neuropathy; lethargy; delirium, coma
c. Cardiopulmonary: pericarditis, myocarditis, pneumonitis, conductional abnormalities, Kussmaul breathing
d. Hematological: anemia, bleeding, immune deficiency, infections
e. Gastrointestinal tract inflammation: stomatitis, gastritis, colitis (may be hemorrhagic)
f. Osteodystrophy: osteitis, osteomalacia, osteoporosis, osteosclerosis
g. Endocrine abnormalities
h. Dermatitis

2. Hyperkalemia: serum potassium levels ~ 6 mmol/L reached acutely or ~ 7 mmol/L reached chronically are often the most urgent life-threatening problem in renal failure as it may be associated with lethal dysrhythmias. Early changes in the EKG include peaked T waves, broadened QRS complexes, prolonged P-R intervals, depressed P waves, low R waves, and bradycardia. These can be reversed with treatment to include calcium, insulin/glucose, exchange resins, inhaled beta-agonists, and bicarbonate. Hyperkalemia which cannot be managed medically is an emergent indication for dialysis.

3. Acidosis: Renal failure leads to hydrogen retention and a metabolic acidosis. It may be necessary to give bicarbonate therapy orally or intravenously if the serum bicarbonate < 20 or the pH < 7.1. When this cannot be done, or if medical management does not ameliorate the acidosis, it may be an indication for dialysis.

4. Volume overload: oliguric or anuric renal failure eventually causes sufficient retention of sodium and water to causes hypertension and/or cardiogenic pulmonary edema. If this is refractory to medical treatment with high-dose diuretics, it may be an indication for dialysis.

5. Intoxication/poisoning with dialyzable drug: Certain ingestions such as ethylene glycol (antifreeze) or overdose of medications such as lithium (a mood stabilizer) can be toxic. High blood levels and associated symptoms may be an indication for rapid removal by dialysis.

II.4. Acute Kidney Injury

II.4.a. Definition of AKI

Acute kidney injury (AKI), also known by the still common term acute renal failure, is a process of extensive loss of renal function occurring over hours-to-days-to-weeks. Depending on the setting, it is associated with mortality rates ranging from 7% (for prerenal azotemia acquired in the community) to as high as 80% (for hospital-acquired AKI requiring ICU care). When AKI presents with oliguria (urine output < 400 mL/day), it usually indicates a more severe injury, and the mortality is 75%, compared with 25% with a nonoliguric presentation. Despite the widespread use of dialysis for supportive care, the mortality rates for AKI have not changed over the past 30 years.
The exact definition of how much renal function must be lost to qualify as “renal failure” has been a source of much controversy over the years. Recent studies suggest that in hospitalized patients, even a small (0.3 mg/dL) increase in the serum creatinine from baseline levels is associated with a significant increase in mortality.

II.4.b. Etiologies of AKI (Key finding approach)
AKI is usually categorized into postrenal, prerenal, and intrinsic renal causes as shown in Table 2 and Figure 1.

<table>
<thead>
<tr>
<th>POSTRENNAL</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Ureteral, bladder and urethral malformations</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Females: pregnancy; uterine prolapse; uterine tumors; ovarian cysts, abscesses, tumors; pelvic inflammatory disease, cervical ca. Males: prostatism, prostate adenocarcinoma</td>
</tr>
<tr>
<td>GI system</td>
<td>Appendicitis, colorectal ca., Crohn’s dz., diverticulitis, pancreatitis</td>
</tr>
<tr>
<td>Vascular system</td>
<td>Aneurysms, ovarian vein thrombophlebitis, retrocaval ureter</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>Fibrosis, hemorrhage, surgical complication, infection, post-radiation therapy, neoplasm</td>
</tr>
<tr>
<td>Intraluminal</td>
<td>Renal calculi, crystalline uropathy, papillary necrosis, clot, fungus ball</td>
</tr>
<tr>
<td>Neurological</td>
<td>Neurogenic bladder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PRERENAL</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular volume depletion</td>
<td>Hemorrhage, vomiting, diarrhea, diuresis, third-spacing, burns, fever</td>
</tr>
<tr>
<td>Decreased cardiac output</td>
<td>CHF, valvular heart disease, pulmonary hypertension</td>
</tr>
<tr>
<td>Decreased renal perfusion with normal/high cardiac output</td>
<td>Sepsis, cirrhosis, renal vein thrombosis</td>
</tr>
<tr>
<td>Drug-mediated hypoperfusion</td>
<td>NSAIDs, ACE inhibitors, angiotensin II receptor antagonists, cyclosporine/tacrolimus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTRINSIC</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>Surgery, shock—cardiogenic, septic, hypovolemic</td>
</tr>
<tr>
<td>Nephrotoxic</td>
<td>Aminoglycosides, amphotericin B, radiocontrast agents, chemotherapeutic agents, cyclosporine/tacrolimus, hemoglobinuria, myoglobinuria</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Primary (idiopathic) and secondary (lupus, infectious) causes</td>
</tr>
<tr>
<td>Tubulointerstitial disease</td>
<td>Allergic interstitial nephritis, crystal nephropathy, multiple myeloma</td>
</tr>
<tr>
<td>Vascular</td>
<td>Cholesterol emboli, thrombotic microangiopathy, vascular trauma/infarct</td>
</tr>
</tbody>
</table>
II.4.c. Prerenal Azotemia

Prerenal azotemia results from the normal neurohormonal responses of the kidneys to a perceived loss of effective circulating arterial volume. The sympathetic nervous and renin-angiotensin-aldosterone systems increase renal afferent and efferent resistances, respectively, in order to preserve arterial volume. Aldosterone and ADH production lead to sodium and water retention in the tubules. Without these responses, the body would not be able to effectively compensate against mild hypovolemia. (One could argue that prerenal azotemia is not “renal failure” at all, but “renal success”!)

The increase in renal arterial resistances leads to decrease in renal blood flow, which tends to decrease GFR. In mild volume depletion, this decrease in GFR is limited though counteraction by local afferent vasodilatory responses (autoregulation), by prostaglandin-mediated afferent vasodilatation, and by an increase in glomerular pressure resulting from efferent vasoconstriction. In severe volume depletion, or when the counteracting mechanisms are antagonized (such as with NSAIDs or angiotensin antagonists), more severe losses of GFR occur.

II.4.d. Acute Tubular Necrosis (ATN)

Discussion of all causes of intrinsic renal failure is beyond the scope of this syllabus, and the reader is referred to the references. Acute tubular necrosis (ATN) deserves special consideration as it is the most frequent cause of AKI other than prerenal azotemia. ATN can occur from many different etiologies, including septic shock, prolonged ischemia, use of nephrotoxins (especially radiocontrast agents and antibiotics) and rhabdomyolysis. The ischemic or toxic exposure leads to a complex combination of inflammation, edema, apoptosis, and necrosis along with sloughing of the tubular epithelium. The damage of to the epithelium causes back leak of tubular fluid into the interstitium and the necrotic debris may case mechanical obstruction of the tubules. If the underlying etiology can be stopped, then the tubules may be eventually able to regenerate over time and kidney function will be restored.

The classic clinical pattern of ATN has four phases:

1. *Injury phase*: usually lasting hours-to-days depending on the length and degree of exposure to the etiology. Treatment consists of supportive care: removing offending agents and ensuring adequate renal perfusion.
2. *Oliguric phase*: lasting days-to-weeks. The patient must be monitored closely for metabolic complications of renal failure and volume overload. For prolonged or severe ATN, dialysis may be needed.
3. *Diuretic phase*: the first sign of impending recovery is usually a brisk diuresis for several days. Despite the high urine output, there is little-to-no improvement in renal function as measured by CrCl.
4. *Recovery phase*: Renal function improves as indicated by a drop in the serum creatinine and normalization of acid-base and potassium status. Depending on the
previous health of the kidneys, there may be gradual improvement to complete recovery or subclinical functional abnormalities.

II.4.e. Diagnosis of Prerenal Azotemia vs. ATN

A very common and important clinical situation is a patient who presents with AKI and the determination of whether it is prerenal azotemia or ATN. Prerenal azotemia, when prolonged, commonly leads to ischemia which contributes to the establishment of ATN. Sometimes the presenting clinical features obtained through history and physical examination are conclusive, but often they are not.

One approach is “diagnosis by therapy”. Quick recovery of renal function after correction of the intravascular volume status confirms prerenal azotemia, since it is a compensatory hemodynamic response to hypoperfusion.

If a more thorough diagnostic assessment is necessary, the urine sediment of a patient with classic ATN often contains sloughed renal tubular epithelial cells and/or granular dark formed elements (“muddy-brown casts”), which represent degenerated cells. Urinalysis may also show an inability to concentrate higher than a specific gravity of 1.011, iso-osmotic with the serum (a condition called isosthenuria), also reflective of tubular dysfunction. A patient with simple prerenal azotemia usually has very little of note in the urine sediment and is able to concentrate urine close to maximum measurable levels (specific gravity 1.030).

Some laboratory diagnostic indices can be helpful in making the distinction. The urinary Na concentration is generally below 20 mEq/L in prerenal azotemia (because the functioning tubules are appropriately retaining sodium to maintain intravascular volume), but above 40 mEq/L in ATN. The diagnostic accuracy of the urinary sodium can be increased by calculating the fractional excretion of sodium (FE$_{Na}$). The FE$_{Na}$ is a clinical index used to measure the tubular reabsorption of sodium:

\[
\text{FE}_{\text{Na}} \text{ (\%)} = \frac{\text{Clearance of Na}}{\text{Creatinine clearance}} \times 100 = \frac{U_{\text{Na}} \times V_{\text{Urine}}/S_{\text{Na}}}{U_{\text{Cr}} \times V_{\text{Urine}}/s_{\text{Cr}}} \times 100 = \frac{U_{\text{Na}} \times s_{\text{Cr}}}{S_{\text{Na}} \times U_{\text{Cr}}} \times 100
\]

$S_{\text{Na}}$, $s_{\text{Cr}}$ = serum sodium (mEq/L) and creatinine (mg/dL)
$U_{\text{Na}}$, $U_{\text{Cr}}$ = urine sodium (mEq/L) and creatinine (mg/dL)
$V_{\text{Urine}}$ = urine volume

A FE$_{Na}$ < 1\% favors the diagnosis of prerenal azotemia, while a value > 2\% favors ATN. The FE$_{Na}$ is elevated in ATN due to a urinary “leak” of sodium, because the damaged renal tubules cannot properly reabsorb the filtered sodium load.

The FE$_{Na}$ may be falsely elevated in a patient who is prerenal but is taking a diuretic. In these circumstances, the fractional excretion of urea (FE-urea), calculated in a manner analogous to the FE$_{Na}$, can be used in its place. A FE-urea of < 35\% is considered diagnostic for prerenal azotemia.
II.4.f. Postrenal AKI
Post-renal AKI is relatively infrequent (1-10% of all AKI), but is always important to consider because it is potentially reversible through surgery or percutaneous procedures. Diagnosis is usually through imaging. A bladder scan (ultrasound) can be done at the bedside and may help determine the presence of urinary retention from an enlarged prostate. A more complete evaluation for obstruction would include a renal ultrasound or CT scan, which may show dilatation of the ureters (hydronephrosis) or the renal pelvis (hydronephrosis), as well as the presence of a stone or other obstructing mass.

II.4.g. Treatment of AKI
Although a medical therapy for established AKI has been much sought-after, one does not currently exist, and because of the protean and often multifactorial nature of AKI, there is unlikely to be a single effective therapy. As such, the most important clinical interventions are early recognition, establishment of etiology, and reversal of the underlying process and/or removal of the offending agent.

In ATN, the damaged renal tubules have the capacity to partially or completely regenerate, and restore renal function, as long as they are not exposed to repeated or prolonged injury. For ICU-associated ATN, which is usually multifactorial, the focus is on treatment of any underlying sepsis, avoidance of hypotensive injury, adjustment of medication doses for level of renal function, discontinuance of nephrotoxins when possible, and supportive management of electrolyte disorders. The proportion of AKI in the ICU which requires dialysis at some point is on the order of 25-60%.

In AKI due to glomerulonephritis and vasculitis, treatment is blood pressure control and--for specific diagnoses--use of immunosuppressive therapies such as prednisone, cytotoxic agents, and plasma exchange.

II.5. Chronic Kidney Disease (CKD)
II.5.a. Epidemiology of CKD
In the United States, 11% of the population (19-20 million people) is believed to have significant (stage 3/4/5) CKD. In 2008, 550,000 people in this country had end-stage renal disease (ESRD): 70% on dialysis and 30% with a functioning transplanted kidney. Having even mild CKD increases morbidity and mortality, particularly from cardiovascular complications.

The leading causes of ESRD in the U.S. are diabetes (40-50%), hypertension (~25%), glomerulonephritis (~10%), and polycystic kidney disease (~3%).

II.5.b. Progression of CKD
The natural history of chronic kidney disease (CKD), regardless of its etiology, is continued loss of renal function over time in the majority of patients. The decline in GFR is believed to be due to changes in renal hemodynamics initiated by the loss of nephrons. When renal mass is reduced, the remaining nephrons undergo hypertrophy,
and the hydraulic pressure in glomerular capillaries rises followed by an increase in the single-nephron GFR. This so-called glomerular hyperfiltration leads to glomerular injury and scarring, ultimately resulting in glomerular obsolescence and setting up a vicious cycle of continuing glomerular damage in the remaining nephrons.

Thus, if renal function is plotted against time (see Figure 2), either as GFR or using 1/sCr as an estimator, there tends to be a linear decrease with time with normal progression of the disease. (The exact slope of the line varies from patient to patient.) Therapeutic strategies to halt or decelerate progression in CKD are designed to attenuate glomerular hyperfiltration (which is usually associated with increased glomerular permeability to plasma proteins, resulting in proteinuria, a hallmark of many types of CKD). The most important therapy is blood pressure control (recommended targets of < 140/90 in patients without proteinuria and < 130/80 in patients with proteinuria). For kidney disease associated with proteinuria (i.e., diabetes and glomerulonephritis), specific pharmacologic blockade of AII action by ACE inhibitors or AII receptor antagonists is recommended. This brings about efferent arteriolar vasodilation and subsequently attenuates hyperfiltration. If these interventions are successful, then the rate of decline of GFR should decrease. On the other hand, if there is a new insult which causes an acute-on-chronic process, the rate of decline increases (see Figure 2).

Figure 3

II.5.c. Stages of CKD
CKD is divided into stages based on GFR, and the complications of CKD grow more with decline in GFR as shown in Table 3. Stage 5 CKD is end-stage renal disease, the point at which dialysis or transplantation is usually recommended.
Progression of CKD is associated with multiple clinical manifestations, which are also shown in Table 3.

Hypertension is associated with even mild kidney disease, and patients with advanced CKD are prone to volume overload which normally manifests as peripheral edema but can be severe enough to cause congestive heart failure.

The kidney plays an important role in regulation of mineral metabolism, and is responsible for conversion of Vitamin D from the 25-hydroxy to the 1,25-hydroxy form. Dysregulation of bone metabolism with secondary hyperparathyroidism and hyperphosphatemia begin to occur with even mild loss of renal function.

The kidney makes erythropoietin, and its production decreases as kidney function falls, resulting in a normochromic, normocytic anemia. Patients on dialysis and some with advanced CKD may receive treatment with recombinant erythropoietin to avoid the need for blood transfusions.

Severe metabolic acidosis and hyperkalemia along with the other systemic complications of uremia are associated with the very late stages of CKD.

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR (ml/min/1.73 m^2)</th>
<th>Hypertension/Hypervolemia</th>
<th>Osteodystrophy</th>
<th>Anemia</th>
<th>Acidosis/Hyperkalemia</th>
<th>Uremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 90</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>60-89</td>
<td>+</td>
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<tr>
<td>3</td>
<td>30-59</td>
<td>++</td>
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<td>4</td>
<td>15-29</td>
<td>+++</td>
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<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

**II.5.d. Diabetic Nephropathy**

Diabetic nephropathy is the #1 cause of CKD in the US, accounting for about 40% of all patients with ESRD. Diabetic nephropathy occurs in about 30-40% of patients with type 1 or 2 diabetes. Nephropathy is associated with other manifestations of microvascular disease (retinopathy, neuropathy, coronary disease). The natural history of type 1 diabetic nephropathy classically follows five stages (see Figure).
Stage 1 is early renal hypertrophy and glomerular hyperfiltration and is associated with absence of microalbuminuria (< 20 mg/d) and an elevated GFR. Stage 2 is without clinically evident disease (other than the elevated GFR) but histologically manifested by glomerular basement membrane thickening and mesangial expansion. Microalbuminuria (> 20 mg/d) presents in stage 3, usually 5-15 years after initial diagnosis. During stage 4, overt nephropathy presents as microalbuminuria and declining GFR, leading to ESRD around 25 years after initial presentation. Histologically, the classic Kimmelsteil-Wilson nodules can be seen, along with nonspecific tubulointerstitial fibrosis. The decline in GFR in stage 4 can be rapid, averaging about 1 ml of GFR per month.

Associated with the progression of renal disease in diabetic nephropathy is the development of retinopathy, neuropathy, and hypertension. The incidence of retinopathy approaches 90% in patients with diabetic nephropathy. For patients with diabetic nephropathy, early (at the first sign of microalbuminuria) and aggressive blood pressure control and use of ACE inhibitors and angiotensin II blocks is a mainstay of therapy. In addition, tight glycemic and lipid control and avoidance of exposure to potential nephrotoxins whenever possible are necessary.

Although the natural history of type 2 diabetic nephropathy is not as well-established as type 1, similar therapeutic recommendations have been shown to be effective at slowing progression.

**III. Basic Approach to Diagnosis**

**III.1. Determine if process is acute vs. chronic vs. acute-on-chronic**

1. Old labs are always your best friend. Plot GFR vs. time if data available.
2. History of known kidney disease or risk factors for CKD.
3. Ultrasound evaluation of kidneys (small, dense kidneys are consistent with CKD).
4. Comparatively limited symptoms in the presence of extreme metabolic derangements (acidosis, elevated blood urea, hyperkalemia, and anemia) suggests adaptation to slow chronic progression rather than rapid acuity.

**III.2. If acute or acute-on-chronic, assess for prerenal vs. postrenal vs. intrinsic renal etiologies**

A. History: assess volume status, look for factors known to decrease renal perfusion, search for known nephrotoxins, look for evidence of systemic diseases (diabetes, rheumatologic/autoimmune diseases)
1. Volume assessment: orthostasis; weight change; intake/output; hx of hypotension, emesis, diarrhea, hemorrhage, burns; CHF symptoms, sepsis, third-spacing (i.e. ascites).
2. Fevers, skin rash, joint/muscle/back pains, pruritis
3. Medications: especially the Big 3—antibiotics, NSAIDs, intravenous contrast. Diuretic and antihypertensive use are also important. Over the counter medications and dietary supplements. Drug allergies.
4. Infectious symptoms.
5. Urinary obstructive symptoms.: frequency, urgency, hesitancy, dribbling, nocturia, frequent urinary tract infections
6. Voiding history: color, volume, dysuria, pattern of output

B. Physical Examination
1. Vitals: including orthostatic VS and weight
2. Skin: torpor, capillary refill, rashes, petechiae, purpura (potential infection, connective tissue disease, or vasculitis)
3. Ocular: uveitis, signs of hypertension or emboli
4. Cardiopulmonary: signs of CHF or hypovolemia, pleural or cardiac rubs
5. Abdominal: palpable bladder, mass, RUQ tenderness, evidence of hepatic disease, bruits
6. Extremities: edema, evidence of tissue ischemia, muscle tenderness
7. Neurosis: mental status, asterixis, cranial nerve palsies

C. Labs
1. Essential: Urinalysis (see Figures 3-7), chemistries, blood count. BUN/Cr > 20 suggests prerenal azotemia.
2. As indicated:
   a. Urine lytes, osmolality, urea, and creatinine:
      i) $U_Na < 1\%$ and/or $FE_Na < 1\%$ suggests prerenal (in absence of diuretic use)
      ii) $Fe$-urea < 35% suggests prerenal.
   b. Urine protein quantitation: either 24-hour collection or spot urine protein/creatinine ratio
   c. Renal ultrasound +/- Doppler studies of arteries and veins: to asses for obstructive process
   d. Echocardiogram: to rule out CHF
   e. Serological assays: when specific primary or secondary glomerulonephritis are suspected (Anti-nuclear antibodies, complements, Anti-neutrophil cytoplasmic antibodies, anti-GBM antibodies, Hepatitis B/C titers, Anti-streptolysin O antibodies)
   f. Invasive hemodynamic measurement for ICU patients where volume status is unknown
   g. Renal biopsy: when glomerulonephritis is suspected
III.3. If chronic or acute-on-chronic, determine cause of chronic disease

Usually established in course of above workup.

IV. Summary

1. Acute and chronic kidney disease have multiple manifestations with a high level of associated morbidity and mortality.
2. Developing the differential diagnosis for acute and chronic kidney disease requires a thorough history and physical examination, urinalysis, and selective laboratory, radiological, and pathological assessment.

Back to the Clinic...

Our patient presents with generalized and non-specific symptoms of relatively rapid onset. These types of presentations should suggest a systemic response to the initiating agent/insult as multiple areas of dysfunction are noted. In these cases and in general, an accurate, detailed, and logically sequence history is essential, including a comprehensive review of all medications, over the counter medications, dietary supplements, herbs, change in diet, and environmental exposure. All appropriate available laboratory data from the acute presentation and from the previous clinic/in-patient encounters should be reviewed. The data collected guides the development of a comprehensive problem list that will serve as the basis for the application of the clinical reasoning skills required to develop a differential diagnosis and plan for further evaluation and treatment.

1. The sequence and course of symptom development must be determined. All prompting stimuli must be determined. The current state of the control of patient’s underlying diseases—diabetes and hypertension—needs to be established. What was the patient's condition in the week preceding the onset of symptoms? In this case, he was presumably well, in his baseline state of health. The most recent laboratories should be reviewed for evidence of ongoing changes that may have been evolving. Knowing the medications a patient is taking is essential, not only to evaluate potential contribution to the clinical presentation but also to determine if doses need to be changed, drugs stopped, and the potential for drug interactions. The patient was recently seen in the clinic: were any new medicines added to his regimen? The patient is taking a thiazide diuretic, beta-blocker, potassium chloride, an alpha-1 blocker (urology), and aspirin. He is also taking a converting enzyme inhibitor, which was started at the last clinic visit.

2. Nausea and vomiting have multiple causes with regard to metabolic causes, in our patient uncontrolled diabetes, gastrointestinal disease, and renal dysfunctions are all potential contributors. The accumulation of metabolic byproducts is a potent stimulus for the reported GI symptoms. Fatigue is also a general symptom and may be a response to the severity of the GI manifestations or reflective of the underlying etiologies suggested.
above. It is also important to consider the potential of a mild encephalopathic state due to metabolic causes. The muscle cramping suggests a potential electrolyte disorder, while the orthostatic response to rising should raise the suspicion of a volume status abnormality and/or lack of an appropriate cardiovascular response to position change. This constellation of symptoms points to an underlying systemic disorder.

3. If one takes an organ system based approach to evaluating the problem list, the contribution of renal dysfunction could explain the majority of the symptoms observed. Acute renal injury results in the accumulation of variety of metabolic end products, the majority of which are products of protein (nitrogen) metabolism. Acid base and electrolyte abnormalities including metabolic acidosis, compensatory respiratory alkalosis, hyperkalemia as well as calcium, magnesium, and phosphate changes are common and occur at various times through the course of the renal insufficiency. The severity and rapidity of their development can provide clues as to the underlying metabolic state of the patient and the duration of the injury. Again, depending on the rapidity of development and the duration of the renal insufficiency and factors such as diet, changes in blood glucose control and blood pressure control may be observed.

4. The primary approach to a patient with suspected renal injury is to a.) Determine the extent of metabolic/electrolyte derangement; b.) Determine the inciting cause of the injury and determine if it is ongoing (drug, obstruction, inflammatory; c.) Correct the most potentially dangerous acid/base and electrolyte abnormalities; d.) Adjust all medication based on the estimated or measured glomerular filtration rate (GFR); e.) Discontinue any medications or other agents that may compromise renal function; f.) Adjust dietary intake to minimize metabolic and electrolyte complications; g.) Based on the severity of the injury and estimate for recovery determine if extracorporeal support (dialysis) is required.

In this patient the creatinine was noted to 5.8 mg/dl from a baseline of 1.2 mg/dl, serum sodium of 122, potassium of 6.5, and a HCO₃⁻ of 13. His EKG showed evidence of ventricular premature contractions and changes compatible with hyperkalemia. The most likely contributing cause of the AKI was the addition of a converting enzyme inhibitor at the last clinic visit to his drug list. This was added to treat the proteinuria. However in this case it caused a significant fall in GFR, hyperkalemia, and diminished blood pressure. Although responses like this are not common with most initial dosages, certain patients appear to be very responsive, particularly those with DM and multiple medications, and require close monitoring and titration of the dose. This patient was also on a thiazide diuretic with potassium supplementation along with a beta-blocker. In addition he had been started on an alpha-1 blocker for his mild obstructive prostatic symptoms in the urology clinic. This drug also can lower blood pressure and affect BP response to changes in posture. The ibuprofen use in the preceding 24 hours may have worsened the severity of the renal lesion. The hyponatremia was considered to be secondary to volume depletion related to the GI symptoms with contributions from the, non-steroidal anti-inflammatory drug use, and increased water intake.

In the ICU
1. AKI in the ICU is often multifactorial, and only by a careful and thorough review of the previous and ongoing medical history can one hope to come to a proper differential diagnosis. In this patient, sepsis or systemic inflammation is a significant risk factor for the development of multi-organ dysfunction, to include kidney failure. The effective circulating blood volume may be diminished by third-spacing or bleeding, leading to hypoperfusion of the kidneys and ischemic injury. Use of vasoactive pressors to maintain central pressures may further decrease renal perfusion. In the case of abdominal trauma, the development of high intra-abdominal pressures may lead to compartment syndrome. In some rare cases, there may be direct traumatic damage to the kidneys, ureters, or bladder. And finally, very frequently kidney injury is precipitated by antibiotics needed to fight infections or by intravenous radiocast used in computed tomography.

2. Most of the diagnostic workup will be through a careful history. A urinalysis is often helpful in determining ATN: the presence of muddy-brown granular casts and renal tubular epithelial cells would support this diagnosis. A low FENa may be helpful in diagnosis of prerenal azotemia. If there is a question of possible postrenal obstruction, a renal ultrasound or noncontrast CT scan is indicated.

3. Therapy consists of removal of the offending agent if one is identified, and avoidance of (or, at least limiting) further nephrotoxic and ischemic insults to the kidney. Surgical intervention may be required if an anatomical problem is found. Dialysis may be indicated in cases of significant metabolic abnormalities or cardiopulmonary compromise.

Practice Questions

1. A 70 year old male presents to the hospital with confusion and is found to have acute kidney failure. If you were considering a diagnosis of glomerulonephritis and you learned that the patient has red blood cell casts in the urine, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely

2. Which of the following findings is not consistent with acute tubular necrosis?
   a. Urine sodium of 10
   b. FeNa of 2%
   c. Muddy brown casts on urinalysis
   d. Urine specific gravity of 1.010

3. True or false: an increase in creatinine from 1.0 to 1.5 is indicative of more significant loss in renal function than an increase from 1.5 to 2.0.

4. Which of the following is the most important therapeutic intervention in slowing the progression of chronic kidney disease?
   a. Smoking cessation
   b. Adequate water intake
   c. Diet and exercise
   d. Blood pressure control

5. Which of the following lab abnormalities is of most immediate life-threatening concern?
a. BUN of 120 mg/dL
b. Serum sodium of 128 mEq/L
c. Serum potassium of 7.5 mEq/L
d. Serum bicarbonate of 16 mEq/L
e. Serum glucose of 320 mg/dL

Answers:
1. The answer is much more likely. The presence of casts is a highly specific (pathognomonic) finding for glomerulonephritis.
2. The answer is a. Patients with ATN and intra-renal failure do not typically have a low urine sodium as they lose the ability to concentrate urine (and thus why their FeNa is >1% and their urine is not concentrated).
3. True. An increase in creatinine from 1.0 to 1.5 represents an approximate change in CrCl from 100 to 67 mL/min (33% loss), while a change from 1.5 to 2.0 is about 67 to 50 mL/min (25% loss).
4. (d). Smoking cessation and diet and exercise are important contributors to cardiovascular health, but blood pressure control is the single most important factor in CKD.
5. (c). Hyperkalemia, especially acute changes, can lead to rapid cardiac conduction disturbances and sudden cardiac death. The other values given are abnormal, but are very unlikely to be immediately life-threatening.
ICR: Kidney Failure Case 1

A 31 year old soldier comes to the Emergency Department complaining of fatigue and diffuse muscle pain. He was previously healthy on no prescribed medications but notes that he had been less physically active than usual for the past few months, and had gained 5 kg. In an attempt to get back in shape and prepare for his upcoming PT test, five days ago he started running and lifting weights and using some dietary supplements given to him by a friend. Three days ago he noticed soreness in his thighs and back for which he has been taking ibuprofen 800 mg three times a day, but the pain has been getting worse over the last day. He has had nausea and two episodes of vomiting over the past 24 hours, but has been eating saltine crackers and drinking water and fruit juices. He denies any chest pain, shortness of breath, fever, chill, and lower extremity edema. He does note that perhaps he is not urinating as frequently.

On examination he looks well but slightly short of breath. Temperature is normal, blood pressure is 165/100, pulse is 86, height is 74 inches and weight is 110 kg. Lungs are clear and heart sounds are normal. He has soreness in his biceps, hamstrings and quadriceps, but no firmness, swelling, or erythema and no edema. He is oriented x 3 and has no asterixis.

Serum:  
- Na=130 mEq/L  
- K=6.6 mEq/L  
- Cl=98 mEq/L  
- Bicarb=10 mEq/L  
- BUN=98 mg/dL  
- Cr=9.6 mg/dL  
- Ca = 8.0 mg/dL  
- Phos = 7.6 mg/dL  
- CPK=212,000

Urine:  
- Specific gravity=1.010  
- protein=1+, blood 3+  
- 2 RBC/HPF, 2 WBC/HPF, 20-30 “muddy”  
- brown pigmented casts/LPF

Urine electrolytes:  
- Na= 50 mEq/L  
- K=15 mEq/L  
- Cr=68 mg/dL

WBC=10,000/mm3  
Hgb=12.4 gm/dL  
Platelets=350,000

Arterial Blood Gas  
- pH=7.26  
- pCO2=22  
- pO2=100

ECG reveals regular rate and rhythm, normal axis and intervals. Tall peaked T waves are seen.
**Case 1 discussion questions:**

1. Construct a problem list for this patient’s presentation, breaking it down into the following categories. Which items on your problem list are of most immediate concern?
   - Signs and symptoms
   - Laboratory abnormalities
   - Contributing medical conditions/past medical history

2. Is this patient suffering from acute or chronic kidney failure? List history, physical, and ancillary clues to support your opinion.

3. Calculate his CrCl using the Cockcroft Gault equation. Does the equation provide an accurate measure of renal function in this circumstance? Calculated the fractional excretion of sodium (FeNa).

4. How does the kidney become involved in muscle injury?

5. How do the following impact the development and/or course of acute renal failure?
   - i) exercise
   - ii) dietary supplements
   - iii) NSAID use
   - iv) content of oral intake

6. What other common classes of medications should you inquire about when evaluating renal failure?

7. List values in the below table which can help differentiate pre-renal from intra-renal acute kidney failure.

<table>
<thead>
<tr>
<th></th>
<th>Pre-renal</th>
<th>Intra-renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN/Cr ratio</td>
<td></td>
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<tr>
<td>Uric acid</td>
<td></td>
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<td>Urine:</td>
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<tr>
<td>Na</td>
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<td>Specific gravity</td>
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<tr>
<td>Sediment</td>
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<tr>
<td>FeNa</td>
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</tbody>
</table>

8. What is this patient’s acid base status at this time?

9. What is the treatment for his hyperkalemia? What is the treatment for his renal failure?

10. What is your differential diagnosis for this patient’s kidney failure? How might the diagnosis change if the sCr was 2.1, the urine sediment was bland, and the urine sodium was 8?
11. List the acute indications for dialysis. Is there a role for dialysis in this case?
Kidney Failure Case 2
Initial Presentation

A 45-year-old African-American Lieutenant Commander presents with a several week history of generalized fatigue, diffuse arthralgias, and “low grade” fever. She also reports malaise and a decreased appetite during this time, though she has gained 7 lbs since symptom onset. She denies chills, night sweats, nausea, vomiting, diarrhea, alopecia, or skin rashes. She also denies chest pain, shortness of breath, PND, or orthopnea.

Medications: acetaminophen as needed, low estrogen birth control pill
Social history: No tobacco, alcohol, history of IVDA or other illicit drug use
Family history: Hypertension-father; Type 2 diabetes-mother

PE: Was essentially normal with the following findings:
BP=160/85, HR=90, RR=18, weight=60 kg
HEENT: pale conjunctivae without scleral icterus
Cardiac: early systolic murmur which does not radiate
Extremities: 2+ ankle and pretibial edema.

Laboratories:
- Na=134 mEq/L
- K=4.9 mEq/L
- Cl=105 mEq/L
- CO2=19 mEq/L
- BUN=42 mg/dL
- Creatinine=2.8 mg/dL (creatinine noted to be 0.8mg/dL at a post-deployment physical 6 months ago)
- Glucose = 104 mg/dL (not fasting)
- Calcium=8.1 mg/dL
- Phos = 6.2 mg/dL
- Albumin= 2.8 mg/dL

Urinalysis: specific gravity=1.018, pH=6, 4+ protein, 2+ blood, glucose neg, leukocyte esterase slightly positive, nitrate neg; sediment: 5-10 dysmorphic RBCs/hpf, 2-4 WBCs/hpf, 0-2 RBC cast/lpf, 1-2 granular casts with renal tubular epithelial cell inclusions/lpf

Case 2 Initial Presentation Discussion Questions:
1. Construct a problem list for this patient’s presentation, broken down into the following categories.
   - Signs and symptoms
   - Laboratory abnormalities
   - Contributing medical conditions/past medical history
2. Calculate her CrCl using the Cockcroft-Gault equation. Does the equation provide an accurate measure of renal function in this circumstance? What is her eGFR from the MDRD equation?

3. Would you characterize her kidney failure as acute or chronic? Provide supporting data: history, physical exam, and/or laboratory data for your answer.

4. What is the differential diagnosis for her kidney failure?

5. What additional tests should be considered and why?

6. Is there a role for a renal biopsy in this case? If so, what are possible findings?

7. What treatments might be considered empirically before a final diagnosis is known? What treatments might be considered after a final diagnosis is known?

---

**Renal Failure Case 2**

**Clinic Presentation 6 Years Post Diagnosis**

After the initial diagnosis and treatment the patient is followed by multiple specialties including nephrology for six years. She comes to see you in the nephrology clinic for a routine follow-up appointment with a history of chronic kidney disease, diabetes, hypertension, and a collagen vascular disease. About one week ago, she developed slight burning when she urinated but this resolved in two days. Three days prior to the clinic visit the burning returned along with a low-grade fever and mild lower abdominal pain. She may have had one chill after taking tylenol the night before the clinic visit but is not sure.

Her current medications include tylenol 325mg prn, oral vitamin D, ramipril 10 mg daily, metoprolol 50 mg twice daily, furosemide 20 mg twice daily, and daily insulin.

On exam, blood pressure is 155/85, pulse 68, weight 62 kg temp 100.8°F otic. Exam shows no jugular venous distention, clear lungs, a fourth heart sound, and no bilateral edema. She has supra-pubic tenderness to deep palpation and mild bilateral costovertebral tenderness to percussion.

**Laboratories:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>136 mEq/L</td>
</tr>
<tr>
<td>K</td>
<td>4.3 mEq/L</td>
</tr>
<tr>
<td>Cl</td>
<td>100 mEq/L</td>
</tr>
<tr>
<td>CO2</td>
<td>20 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>44 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.8 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>143 mg/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>11.8</td>
</tr>
<tr>
<td>Hgb</td>
<td>10.2 g/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>296,000</td>
</tr>
</tbody>
</table>
Calcium=9.1 mg/dL  
Phos = 5.6 mg/dL  
Albumin= 3.5 mg/dL  

Urinalysis: specific gravity=1.013, pH=7, 3+ protein, 3-5 hyaline casts/lpf, 10-15 WBCs hpf, 2 WBC casts seen, leukocyte esterase positive, nitrite positive, numerous bacteria noted  
Urine electrolytes: Na = 38 mEq/L, Creatinine = 68 mg/dL, urea = 245 mg/dL  

Review of her labs shows the following:  
<table>
<thead>
<tr>
<th>Date</th>
<th>Serum creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 years ago</td>
<td>0.8</td>
</tr>
<tr>
<td>5.5 years ago</td>
<td>2.8 (time of hospitalization)</td>
</tr>
<tr>
<td>5 years ago</td>
<td>1.2 (after six months of immunosuppressive therapy)</td>
</tr>
<tr>
<td>3 years ago</td>
<td>1.6</td>
</tr>
<tr>
<td>1 year ago</td>
<td>1.9</td>
</tr>
<tr>
<td>6 months ago</td>
<td>2.0</td>
</tr>
<tr>
<td>Today</td>
<td>3.8</td>
</tr>
</tbody>
</table>

**Case 2 Clinic Visit Discussion Questions:**  
1. Construct a problem list for this patient’s presentation  
2. How would you characterize the kidney failure in terms of acute vs. chronic. Provide supporting data for your answer. Construct a plot of 1/Creatinine vs. time.  
3. Does the FENa help in this case? Why or why not? What other data may be considered in place of the FENa?  
4. Why has her creatinine continued to rise through the 5 years since her initial diagnosis?  
5. What is the differential diagnosis for her acute renal failure?  
6. What additional tests would you consider based on your differential diagnosis?  
7. What would be your initial therapy?
KIDNEY FAILURE: Considerations in the Pediatric population…

CASE: You are asked to see a 2 year-old toddler in the Emergency Room. His parents are worried because he has been acting tired all day and this evening he didn’t want to leave the couch to eat dinner or play with his toys. His parents tell you that he has never been this sick before and deny any possible sick contacts, but state that he had some bloody diarrhea for a couple days earlier in the week. You ask the parents about his urine output and are surprised that he has been wearing the same dry diaper since this morning. On exam, the boy’s vital signs are: Temp 37.0°C, HR 168/min, RR 28/min, BP 98/56, and oxygen saturation of 96% on room air. He is sleeping in his mother’s arms and occasionally opens his eyes when you ask him questions about the train on his tee shirt. His face and conjunctivae appear pale. The boy’s neck is supple and without lymphadenopathy; tympanic membranes are pearly grey and non-bulging; mucous membranes are moist and the posterior oropharynx is without erythema or exudate. His lung exam is normal but you hear a Grade III/VI flow murmur at the left upper sternal border. On abdominal exam, his belly is soft but his liver edge is palpable 3 cm below the right costal margin and his spleen feels enlarged. His skin exam is without any rash or lesions. What could be causing this child’s illness?

Like in adults, a significant decrease in glomerular filtration rate (GFR) or in tubular function is designated as acute kidney injury. GFR is a function of age and body size. Glomerular filtration begins during the third month of gestation and glomerulogenesis is completed at about 34 weeks of gestation. Creatinine clearance is only 40 mL/min/1.73 m² in the full-term newborn and does not achieve adult values (110-125 mL/min/1.73m²) until the child is about 2 years-old. Because creatinine is produced from muscle metabolism and children have less muscle mass than adults, they tend to have lower blood creatinine levels than adults. Although an adult with a creatinine level of 1.0 mg/dL is considered normal, it likely represents renal insufficiency in a 6 month-old. Calculating GFR (expressed as mL/min) in pediatrics can be performed by using an alternative equation, known as the Schwartz formula:

\[ CrCl \approx \left( \frac{k \times Ht}{Cr_{serum}} \right) \]

where height (Ht) is measured in centimeters, serum creatinine (Cr_{serum}) is measured in mg/dL, and the constant \( k \) depends on the age of the child. For term infants < 1 year, \( k = 0.45 \); for a child or adolescent girl, \( k = 0.55 \); for an adolescent boy, \( k = 0.70 \)

Acute kidney injury is less common in children than in adults. One major risk factor for developing acute renal failure is having pre-existing chronic kidney disease. Children rarely have underlying chronic renal disease from conditions such as uncontrolled hypertension or diabetes. A previously healthy child who is placed on vancomycin to treat a hematogenously-spread MRSA osteomyelitis or receives intravenous contrast prior to a CT scan may more easily tolerate these potentially nephrotoxic agents than the diabetic adult with nephropathy.

Like adults, children have pre-renal, intrinsic renal, and post-renal causes of acute renal failure. Pre-renal causes are the most common, such as a child who develops a decrease in circulating blood volume following severe stool losses from an infectious gastroenteritis. If the underlying
cause of inadequate kidney perfusion is reversed, then the child’s renal function usually returns to baseline.

Hemolytic uremic syndrome (HUS) is one of the most common causes of acute kidney injury in young children in the United States and is characterized by the triad of nephropathy, thrombocytopenia, and microangiopathic hemolytic anemia. Verotoxins from the *E.coli* strain O157:H7 or other toxin-producing bacteria damage the vascular endothelium (particularly within the glomeruli) and result in deposition of fibrin and cellular debris, followed by localized clotting and platelet activation. Anemia results from shearing of red blood cells as they pass through the damaged microvasculature.

The etiology of chronic renal failure in children is largely different from adults and depends on the age of the patient. Between birth and 10 years of age, congenital and obstructive abnormalities are the most common causes such as posterior urethral valves in boys. After age 10, acquired diseases such as reflux nephropathy, chronic glomerulonephritis, polycystic disease, or focal segmental glomerulosclerosis become more important causes. Growth failure and progressive delays in bone age before puberty are common in children with chronic renal failure due to impaired vitamin D metabolism and disruptions in calcium and phosphorus homeostasis.

**Back to the case:**

*In your differential diagnosis for this child, you consider inflammatory bowel disease, leukemia, intussusception, bacterial gastroenteritis, appendicitis, sepsis with DIC, or even acute bacterial endocarditis. You order a CBC and basic metabolic panel, which reveals the following: WBC of 19,000, hemoglobin of 7.4 g/dL, and a platelet count of 52K; Sodium 135, potassium 5.7, chloride 100, bicarbonate 17, glucose 98, creatinine 2.1 mg/dL. You review the peripheral smear and notice many schistocytes and helmet cells. Based on these histologic findings and the triad of anemia, thrombocytopenia, and uremia in a patient who had a preceding episode of bloody diarrhea, you speculate that this child has hemolytic uremic syndrome. You later determine that the child had consumed an undercooked hamburger contaminated with *E.coli* O157:H7 from a high school football concession stand.*
Introduction to Clinical Reasoning: Acid-Base
James D Oliver, MD, PhD

**Case:** A 67-year-old man who lives alone is brought to the emergency room with a two-day history of nausea and copious vomiting, severe abdominal pain, and increased shortness of breath. He has known moderate dementia, significant chronic obstructive pulmonary disease, severe painful osteoarthritis, and type II diabetes. He self medicates. His son calls him daily, checks his medicine when he visits about three times a week. The history you obtain is based information from both the patient and the son.

**Questions:**
1) What features of the patient’s history are of particular importance?
2) How would the physical exam help identify causes and consequences.
3) What are the possible acid-base abnormalities?
4) What diagnostic tests would be most useful in determining answers to question 3?
5) What various therapeutic interventions can be anticipated?
6) What if the patient was on chronic diuretic therapy?

**Objectives:** At the end of this session, students will be able to:
1. Discuss normal acid-base physiology (pH regulation)
2. Determine primary acid-base disorders based on clinical information and arterial blood gas data (acidosis vs. alkalosis, metabolic vs. respiratory).
3. Determine the existence of appropriate compensation (using compensation formulas and clinical clues) versus the presence of a secondary disorder in a patient with a primary acid-base disorder.
4. Calculate the anion gap and know the causes of wide anion gap metabolic acidosis (“MUDPILES”)
5. Be able to distinguish chloride-resistant from chloride-responsive metabolic alkalosis.
6. Synthesize clinical data to provide a relevant differential diagnosis for primary and secondary disturbances of pH regulation.
I. Key Definitions

1. **Acidemia/Alkalemia**: a state of increased (acidemia) or decreased (alkalemia) hydrogen ion concentration in the blood.
2. **Acidosis/Alkalosis**: a process which causes acidemia or alkalemia, respectively.
3. **Anion Gap**: a derived parameter which estimates the concentration of unmeasured anions in a body fluid, useful in formulating the differential diagnoses.
   a. Serum Anion Gap: \[ [Na^+] - [Cl^-] - [HCO_3^-] \]
   b. Urine Anion Gap: \( (U_{Na^+} + U_{K^+}) - U_{Cl^-} \)

This topic will illustrate physiologic mechanisms and relevant pathophysiology to understanding acid-base disorders. A stepwise approach (heuristics) and key findings will be emphasized.

II. Basic Science Highlights

**II.A. Normal pH Regulation**

Regulation of acid-base balance is achieved through control of the plasma hydrogen ion concentration \([H^+]\).

The pH is the negative logarithm of \([H^+]\). Under normal conditions \([H^+]\) varies little from the normal value of 40 nm/L, which correlates to a pH = 7.4. Under normal conditions, the pH is maintained between a tight range 7.35-7.45 (\([H^+] = 45-35 \) nm/L). Extreme values of 6.8 and 7.8 (\([H^+] = 160 \) and 16 nm/L) are likely fatal.

The source of hydrogen ion is predominantly from protein metabolism. A typical North American diet results in the generation of about 1 mmol/kg/day of acid as illustrated in figure 1.
The key parts of Figure 1:

1. Dietary intake provides ~ 20 mmol/day of acid (= 20 mEq/day of hydrogen ion).
2. The GI tract excretes 10 mmol/day of base (which is equivalent to the creation of an additional 10 mmol/day of acid).
3. Metabolism produces 40 mmol/day of acid and 15K mmol of CO₂/day.
4. The 15K mmol of CO₂ is expired in the lungs, therefore the net of steps 1+2+3 is the creation of 70 mmol/day of acid that must be excreted in urine.

Note that to excrete 70 mmol/day of acid, three things must happen in the kidney.

1. All 4320 mmol/day of bicarbonate which is passively filtered into the tubules must be reabsorbed (most of which happens in the proximal tubule).
2. 70 mmol/day of “new” bicarbonate must be created (mostly proximal tubule).
3. Acid must be excreted in the form of 30 mmol/day titratable acids (created in the proximal and distal tubule) and 40 mmol/day ammonium (created in the distal tubule).

Changes, disruptions, or imbalances in any of the enumerated steps above can result in alterations of the overall acid-base status.

Tight control of body pH requires coordination between a) the body’s endogenous buffers (bicarbonate/carbon dioxide, phosphates, anionic proteins, hemoglobin, and bone), which work rapidly to prevent alterations by acutely exchanging acid or base loads but which also have a limited capacity, b) the kidneys and c) the lungs (and to a lesser extent, the GI tract). The kidneys, lungs, and bowel ultimately must eliminate acid (or alkali when
necessary) from the body before the endogenous buffering capacity becomes overwhelmed.

Increased \([H^+]\) (pH < 7.4) is blood is termed \textit{acidemia}, and a process which causes acidemia is called an acidosi. Similarly, decreased \([H^+]\) (pH > 7.4) is \textit{alkalemia}, and a process which causes that is an alkalosis. \textbf{The cause of an acidosis or alkalosis may be either metabolic or respiratory in origin.}

The process of \(H^+\) regulation involves three basic steps:

1. \textit{Chemical buffering by the extracellular and intracellular endogenous buffers.} Buffers counteract the pH change induced by addition of an acid (proton donor) or base (proton acceptor) to a solution. The bicarbonate/carbonic acid buffer is the predominant buffer in the extracellular fluid. The equilibrium between pCO2, \(HCO_3^-\), and \(H^+\) can be mathematically defined by the Henderson-Hasselbach equation:

\[
pH = pK + \log \left( \frac{HCO_3^-}{0.03 \times pCO_2} \right)
\]

For the purpose of evaluating the acid-base status of a patient, this equation can be simplified to the following relationship:

\[
pH \propto \frac{HCO_3^-}{pCO_2}
\]

In other words, the ratio of \(HCO_3^-\) to pCO2 defines the pH. Normally, plasma bicarbonate is 24 mEq/L and normal pCO2 = 40 mmHg (equal to 1.3 mEq/L of carbonic acid). Thus the normal base/acid ratio is 20:1.

2. \textit{Control of the CO2 level in blood by alterations in the minute ventilation.} Acidemia, through central and peripheral chemoreceptors, stimulates respiration which leads to an increased elimination of CO2 by the lungs.

3. \textit{Control of bicarbonate concentration in the blood by changes in renal \(H^+\) excretion.} The kidneys are responsible for regulation of serum [\(HCO_3^-\)]. Bicarbonate filtered at the glomerulus is reabsorbed, and new bicarbonate is generated in the distal nephron. The latter involves an active \(H^+\)-ATPase pump plus buffering of the secreted \(H^+\) by ammonia and other urinary buffers.

Disruptions in any one of the above three steps will lead to compensatory changes in the other two in an attempt to maintain normal base/acid ratio and pH. The ratio \(HCO_3^-/pCO_2\) can be used to predict the compensation to a primary acid-base disturbance. When there is a primary alteration in the metabolic status (\(HCO_3^-\), numerator), the body normally will compensate through respiratory mechanisms (pCO2, denominator) in order to maintain the acid/base ratio close to 20:1 and keep pH close to normal. Thus a change in \(HCO_3^-\) in one direction will result in a change in pCO2 in the same direction. Similarly, a primary alteration in the respiratory status (changes in pCO2) will lead to
compensation (changes of $\text{HCO}_3^-$ in the same direction) through metabolic mechanisms. These are discussed in detail in the following section.

Compensation does not completely correct for the primary acid-base disturbance thus, there is always at least a small residual deviation from normal pH in simple acid-base disorders. Overwhelming of the capacity for compensation will ultimately lead to abnormal $\text{HCO}_3^−/\text{pCO}_2$ ratios and thus more significant changes in pH.

**Categories of Acid-Base Disorders ( Syndromes)**

**II.B. Metabolic acidosis**

Metabolic acidosis is usually the most clinically significant diagnosis to make in acute illness but is also procedurally the most difficult to do. Metabolic acidosis has numerous causes as outlined below in Table 1. Three general mechanisms cause metabolic acidosis: 1) increased $\text{H}^+$ production, 2) decreased $\text{H}^+$ excretion, and 3) excess bicarbonate loss (usually through the kidneys or GI tract).

<table>
<thead>
<tr>
<th>Causes of Metabolic Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anion-gap metabolic acidosis</strong></td>
</tr>
<tr>
<td>• Lactic acidosis</td>
</tr>
<tr>
<td>• Ketoacidosis (diabetic, alcoholic, starvation)</td>
</tr>
<tr>
<td>• Poisonings (ethylene glycol, methanol, salicylates, paraldehyde)</td>
</tr>
<tr>
<td>• Pyroglutamic acidosis</td>
</tr>
<tr>
<td>• Uremia</td>
</tr>
<tr>
<td><strong>Non-anion gap (hyperchloremic) acidosis</strong></td>
</tr>
<tr>
<td>• Renal tubular acidosis</td>
</tr>
<tr>
<td>• Diarrhea</td>
</tr>
<tr>
<td>• Pancreatic/biliary secretory losses</td>
</tr>
<tr>
<td>• Ureteral-ileal/colonic diversions</td>
</tr>
<tr>
<td>• Normal saline infusions</td>
</tr>
</tbody>
</table>

Acidemia stimulates ventilation and blowing off of $\text{CO}_2$ in the lungs. This respiratory compensation partially, but not completely, restores pH towards normal levels.

\[
\downarrow \text{pH} \propto \downarrow \downarrow \text{HCO}_3^- \downarrow \text{pCO}_2 \leftarrow \text{disturbance} \leftarrow \text{compensation}
\]

Inability to compensate will result in the pH deviating even farther from baseline. When one has determined that a primary metabolic acidosis exists, it is necessary to check for appropriate respiratory compensation. If compensation is not impaired (as might be seen in lung disease or neurological respiratory impairment), then the $\text{pCO}_2$ does not fall sufficiently and a secondary disorder (respiratory acidosis) is present. In rarer cases, it is
possible to see overcompensation where the pCO2 is lower than would be expected for compensation and the secondary disorder is a respiratory alkalosis.

**After determining the presence of a metabolic acidosis and the degree of compensation, the next step is to determine the presence or absence of the anion gap (AG).** The AG is a useful clinical concept in the differential diagnosis of metabolic acidosis. The body must adhere to electroneutrality; therefore the sum of all positive charges must equal those of negative charges. The AG refers to the difference between the plasma concentrations of the major cation (Na⁺) and anions (Cl⁻ and HCO₃⁻)

\[
AG = [Na^+] - [Cl^-] - [HCO_3^-].
\]

In normal conditions, the AG = 12±3 mEq/L. Most of the anion gap is due to albumin, with the rest consisting of other anionic proteins, phosphates, sulfates, and small amounts of organic acids such as lactate. Elevations of the anion gap above normal suggest the presence of an excess amount of acid, either of endogenous (produced by the body such as in lactic acidosis or ketoacidosis) or exogenous (ingestions such as salicylates or methanol) origin. A common **mnemonic** for the differential diagnosis of elevated anion gap metabolic acidosis is “**MUDPILES**”: methanol, uremia, diabetic ketoacidosis (also starvation/alcoholic ketoacidosis), paraldehyde/pyroglutamic acid, iron/isoniazid, lactic acidosis, ethylene glycol, and salicylates.

The Gamblegram (created by Dr. James Gamble in 1939) is a useful schematic for illustrating the relationship between electroneutrality and the anion gap. As shown in Figure 2, the normal anion gap of 12 exactly balances the normal sodium concentration with that of the major anions. In a pure elevated anion gap acidosis (middle columns in Figure 2), the concentration of bicarbonate is lowered by exactly the same amount (8 mEq/L) that the anion gap is increased. Alternatively, acidosis can occur without an elevation of the anion gap. In this instance (right columns of Figure 2), the chloride concentration is increased by 8mEq/L, resulting in the same degree of acidosis ([HCO₃⁻] = 16 mEq/L). **Thus a normal-anion gap metabolic acidosis (NAGMA) is also called a hyperchloremic metabolic acidosis.** Processes which cause NAGMA are those in which excessive bicarbonate is lost from the body (e.g., diarrhea and renal tubular acidosis, see Table 1).

Many clinical scenarios result in the combination of an elevated anion gap metabolic acidosis plus a separate metabolic process (either acidosis or alkalosis). The purpose of the “delta-delta” formula, described subsequently, is to help diagnose these situations.
II.B.1. Important Considerations on the Anion Gap

The important thing to remember about the anion gap is that it is a man-made artificial quantity, not a physiological one. The body is concerned with regulation of pH, not the anion gap. If we could quickly measure all serum cations and anions there would be no need to determine an anion gap. Remember also that acidosis is not caused by the constituents of the anion gap, but by its associated hydrogen ions.

The AG should be thought of as a clinical “index of suspicion” for the presence of an excess anion. A normal AG is 12 mEq/L. An AG ≥ 16 should raise suspicion for one of the causes of elevated AG acidosis, though we may not always be able to identify it. An AG of ≥ 20 is usually considered an “absolute” anion gap, meaning that there is definitely an excess anion present and one should nearly always be able to figure out what it is. The larger the anion gap, the higher the probability of making the diagnosis.

Finally, remember that the bulk of the anion gap is due to serum proteins, especially albumin. Therefore, when hypoalbuminemia is present, the “normal” value for the AG decreases. The usual correction factor is 2.5 per 1 mg/dL; that is, if a normal AG of 12 corresponds to a normal serum albumin of 4 mg/dL, then at an albumin = 3 mg/dL the normal AG is 9.5 and at an albumin = 2 mg/dL the normal AG is 7.
II.B.2. Renal Tubular Acidosis

The renal tubular acidoses (RTAs) are a family of inherited and acquired disorders which lead to normal-anion gap metabolic acidosis. Proximal (type II) RTAs are due to impaired proximal reabsorption of bicarbonate and can be seen in association with many toxins and disease that affect the proximal tubule. Distal (type I) RTA is a result of impaired ammonium excretion. An important clinical clue suggesting the presence of a distal RTA is when the urine is not maximally acidified (pH > 5.3) despite the presence of a metabolic acidosis. Hyperkalemic Distal (type IV) is a common form of RTA associated with hypoaldosteronism, diabetes, and renal insufficiency. It is distinguished from types I and II by the presence of mild-to-moderate hyperkalemia. Clinical features of the major RTAs are summarized in Table 2.

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Proximal (type II)</th>
<th>Distal (type I)</th>
<th>Hyperkalemic Distal (type IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarb reabsorption</td>
<td>Acid secretion</td>
<td>K+ and acid secretion</td>
<td></td>
</tr>
<tr>
<td>Urine pH</td>
<td>&lt; 5.5 normally</td>
<td>&gt; 5.3</td>
<td>&lt; 5.3 usually</td>
</tr>
<tr>
<td>Urine chemistries/sediment</td>
<td>Glycosuria, aminoaciduria, phosphaturia, uric acid crystals</td>
<td>Calcium crystals</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>Urine ammonium excretion (urine anion gap)</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum bicarb</td>
<td>Usually 14-18 mEq/l</td>
<td>Can be &lt; 10 mEq/L</td>
<td>Usually 15-20 mEq/L</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Hypokalemia</td>
<td>Hypokalemia (severe)</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>High bicarb excretion after normalization of serum bicarb</td>
<td>Acidosis + high urine pH + Positive UAG</td>
<td>Positive UAG + hyperkalemia</td>
</tr>
<tr>
<td>Common causes</td>
<td>Inborn metabolic errors, Fanconi syndrome, Nephrotic syndrome, Transplant rejection, paraproteinemias, Drugs/Toxins: outdated tetracycline, Cd, Hg, Pb, U, Acetazolamide, Mafenide</td>
<td>Inborn metabolic errors, Nephrocalcinosis, hypercalcemia, myeloma Connective tissue diseases/Autoimmune, hyperthyroidism, renal transplant rejection, Drugs/Toxins: amphotericin, toluene</td>
<td>Hypoaldosteronism (diabetes), pseudohypoaldosteronism, Chronic interstitial nephritis, renal transplant rejection, obstructive nephropathy, Drugs/toxins: miloride, Lithium, spironolactone, triamterene</td>
</tr>
<tr>
<td>Treatment</td>
<td>Bicarb (10-25 mmol/kg/day) and K repletion, Vitamin D</td>
<td>Bicarbonate (1-1 mmol/kg/day)and K repletion</td>
<td>Fludrocortisone if indicated Diuretics, bicarbonate</td>
</tr>
</tbody>
</table>

When a NAGMA due to distal (type I or IV) RTA is suspected, diagnosis can be made by demonstrating impaired urinary ammonium excretion. Since very few laboratories are capable of measuring urine ammonium directly, it is indirectly measured by the urinary anion gap: UAG = (U_{Na} + U_{K}) − U_{Cl}. Put another way, the UAG = (unmeasured anions – unmeasured cations). In a normal acid-base state, the UAG is +30 to +50 mEq/l. In metabolic acidosis with normal kidney function, the urine ammonium concentration (unmeasured cations) will increase and the UAG should be −30 to −50 mEq/l. A positive UAG in metabolic acidosis is indicative of inappropriately low ammonium excretion, i.e., distal RTA.

Clinically, RTA can present in a patient in a manner similar to diabetic ketoacidosis, i.e., polyuria with metabolic acidosis. The initial key to diagnosis (other than the normal
serum glucose) is distinguishing between an elevated anion gap (suggesting ketoacidosis) versus a normal anion gap (consistent with RTA).

**II.C. Respiratory Acidosis**

Respiratory acidosis results from CO₂ retention due to impaired respiratory function. Since CO₂ diffuses rapidly, the abnormality is caused by insufficient ventilation (often due to bronchial obstructive physiology) rather than loss of lung parenchyma. Causes of respiratory acidosis are listed in Table 3. The common denominator is hypoventilation causing CO₂ retention.

<table>
<thead>
<tr>
<th>Causes of Respiratory Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airway obstruction</strong></td>
</tr>
<tr>
<td>• Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>• Asthma</td>
</tr>
<tr>
<td>• Foreign body aspiration</td>
</tr>
<tr>
<td><strong>Musculoskeletal disorders</strong></td>
</tr>
<tr>
<td>• Muscle weakness (e.g., hypophosphatemia, myasthenia gravis, amyotrophic lateral sclerosis)</td>
</tr>
<tr>
<td>• Severe obesity</td>
</tr>
<tr>
<td>• Chest wall abnormalities (e.g., scoliosis)</td>
</tr>
<tr>
<td><strong>Central respiratory depression</strong></td>
</tr>
<tr>
<td>• Drugs (e.g., opiates)</td>
</tr>
<tr>
<td>• Oxygen therapy in chronic hypercapnia</td>
</tr>
<tr>
<td><strong>Mechanical hypoventilation</strong></td>
</tr>
</tbody>
</table>

In analogous fashion to metabolic acidosis, a respiratory acidosis leads to a metabolic compensatory response by the kidneys, which partially corrects the pH.

\[
\text{↓ } pH \quad \propto \quad \text{↑ } HCO_3^- \quad \uparrow \downarrow \text{pCO}_2 \quad \Leftarrow \text{compensation} \quad \Leftarrow \text{disturbance}
\]

Unlike with metabolic acidosis, where the respiratory compensation happens immediately, with respiratory acidosis the metabolic compensation occurs in two separate phases: An early acute compensation due to endogenous cellular buffering occurs within minutes-to-hours, while a chronic and more robust compensation due to increased renal acid secretion occurs within 3-to-5 days. Impairment in renal function may lead to a diminished ability to compensate.

**II.D. Metabolic Alkalosis**

Metabolic alkalosis results when urinary or gastrointestinal loss of hydrogen ion occurs or when there is total-body gain of alkali. Common causes are listed in Table 4.
Urinary/gastrointestinal loss of hydrogen ion usually occurs as HCl, thus the increase in bicarbonate occurs in conjunction with a near-equal decrease in serum chloride. Clinical signs of volume depletion and a low urine chloride concentration (< 20 mEq/L) are often associated with this condition. Because it can be treated by infusion of chloride (usually in the form of NaCl), this is known as chloride-responsive metabolic alkalosis.

Total-body gain of alkali usually results from exogenous administration of bicarbonate or states of mineralocorticoid excess. Hypokalemia is also often present.

Alkalosis decreases the respiratory drive so a compensatory retention of CO₂ occurs. The direction of changes in serum bicarbonate and pCO₂ are the same as seen in respiratory acidosis; the difference is that the ratio of the changes result in an increase rather than a decrease in pH.

\[ \uparrow pH \propto \uparrow\uparrow HCO_3^- \quad \uparrow pCO_2 \quad \leftarrow \text{disturbance} \quad \leftarrow \text{compensation} \]
### II.E. Respiratory Alkalosis

Respiratory alkalosis results from hyperventilation. Causes are both pulmonary and extrapulmonary and are listed in Table 5. When hypoxia increases ventilation, CO₂ is blown off excessively. Similarly, neurological abnormalities or anxiety can cause hyperventilation.

The direction of changes in serum bicarbonate and pCO₂ are the same as seen in metabolic acidosis; the difference is that the relative magnitude of the changes result in an increase rather than a decrease in pH:

\[
\uparrow pH \propto \downarrow HCO_3^- \downarrow \downarrow pCO_2 \leftarrow \text{compensation} \leftarrow \text{disturbance}
\]

As with respiratory acidosis, the metabolic compensation occur both acutely (minute-to-hours) and chronically (3-to-5 days). The chronic compensation results both from less bicarbonate reabsorption and less ammonium secretion in the kidney.

### III. Basic Approach to Diagnosis

#### III.A. Overview

A key to diagnosis of acid-base disorders is to adopt a systematic approach to analyzing the numbers and then consistently use that same approach for every problem. Most systems are variants of the method presented here.
The data available usually consists of clinical information (history and physical), an arterial blood gas (minimum: pH and pCO₂; may also include pO₂ and calculated bicarbonate) and serum electrolytes ([Na⁺], [Cl⁻], [HCO₃⁻]). In specific cases, additional results such as urine electrolytes may be available.

The analysis consists of the following steps:

1. Evaluate the laboratory data:
   a. Determine the primary acid-base disturbance.
   b. Determine if there is expected and appropriate compensatory response for the primary disturbance.
      i. If the compensation is too little or too much, then you have identified at least one secondary disturbance.
   c. Look for the presence of an elevated anion gap and additional secondary disturbances.
      i. If an anion gap is present, look for additional secondary metabolic disturbances (i.e., a concomitant non-anion gap acidosis or metabolic alkalosis) using the “delta-delta”.
   d. Summarize the primary and secondary disturbances you have found based on the laboratory data

2. Evaluate the clinical scenario
   a. Determine the cause of each disturbance using the clinical scenario.
      (Refer to the differential diagnosis given previously in the tables of this handout.)

3. Develop a treatment plan.

More experienced clinicians will first summarize the clinical scenario and may anticipate the acid-base derangements associated with them even before looking at the lab data. Table 6 lists typical acid-base disorders seen in some common clinical presentations.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Metabolic acidosis</th>
<th>Metabolic alkalosis</th>
<th>Respiratory acidosis</th>
<th>Respiratory alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIOVASCULAR DISEASE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary arrest</td>
<td>AG</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>CNS disease</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
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<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>DRUGS</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Poisonings</td>
<td>AG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fever</td>
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<td>✓</td>
</tr>
<tr>
<td><strong>GI DISEASES</strong></td>
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<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>NAGMA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vomiting/gastric suction</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>AG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>NAGMA</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hypokalemia</td>
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<td>✓</td>
</tr>
<tr>
<td><strong>PULMONARY DISEASE</strong></td>
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<td></td>
</tr>
<tr>
<td>Acute asthma</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Emboli</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>RENAL DISEASE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>AG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Renal tubular acisosis</td>
<td>NAGMA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sepsis</td>
<td>AG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
IIIB. Detailed Approach

1. We assume that “normal” values are pCO2 = 40 mmHg, [HCO3−] = 24 mEq/L and AG = 12 mEq/L.

2. Determine the primary disorder from the pH and pCO2 (remember pH α HCO3−/pCO2):

   Primary metabolic disturbance: arrows move in same direction
   - pH ↑, pCO2↑ = metabolic alkalosis
   - pH ↓, pCO2↓ = metabolic acidosis

   Primary respiratory disturbance: arrows move in opposite directions
   - pH ↑, pCO2↓ = respiratory alkalosis
   - pH ↓, pCO2↑ = respiratory acidosis

3. Calculate the expected compensation for the primary disorder: This is where it gets a bit sticky, especially when you have to distinguish between acute and chronic metabolic compensations to primary respiratory disturbances. There are many different variants on the compensation formulas given below, but they all attempt to do the same thing. If you find the ones below difficult to use, feel free to find a system you are comfortable with and stick to it. In the method below, we calculate an “expected” value and compare to the actual measured one. For a primary metabolic disturbance, an “expected” pCO2 (epCO2) is compared to the actual value. For a primary respiratory disturbance, “expected” e[HCO3−] are calculated for both acute and chronic cases and compared to the actual value.

   For primary metabolic disturbance, calculate epCO2:
   - Metabolic acidosis: epCO2 = (1.5* [HCO3−] + 8) ± 2 ("Winters’ formula")
   - Metabolic alkalosis: eΔpCO2 = 0.6*Δ[HCO3−], epCO2 = 40 + eΔpCO2

   For primary respiratory disturbance, calculate e[HCO3−] = 24 + eΔ[HCO3−]
   - Respiratory acidosis: eΔ[HCO3−] = 0.1*ΔpCO2 (acute)
   - eΔ[HCO3−] = 0.35*ΔpCO2 (chronic)
   - Respiratory alkalosis: eΔ[HCO3−] = 0.2*ΔpCO2 (acute)
   - eΔ[HCO3−] = 0.5*ΔpCO2 (chronic)

4. Compare the calculated expected compensated value with the actual measured value. If expected compensated value ≠ measured value, then you have a secondary process. For example, if you have a primary metabolic acidosis, and the epCO2 is lower than the actual pCO2, then there is a secondary respiratory acidosis in excess of the expected compensatory response.

5. Calculate the serum anion gap: AG = [Na+] −[Cl−] −[HCO3−]
   a. Only if the anion gap is elevated, determine if there is also an additional metabolic alkalosis or non-anion gap metabolic acidosis. There are
several ways to do this, but the most common is known as the “delta-delta” method.

i. Calculate the change in the AG from “normal” (usually =12).
$$\Delta AG = AG - 12$$

ii. Calculate the different in the measured bicarbonate from “normal” (usually =24).
$$\Delta [HCO_3^-] = 24 - \text{measured}[HCO_3^-]$$

iii. Compare $\Delta AG$ to $\Delta [HCO_3^-]$ (remember Figure 2)
   1. If $\Delta AG = \Delta [HCO_3^-]$, then the elevated anion gap completely explains the change in bicarbonate, and there is no additional process.
   2. If $\Delta AG > \Delta [HCO_3^-]$, then the change in bicarbonate is less than the change in anion gap, and there must be an additional metabolic alkalosis present.
   3. If $\Delta AG < \Delta [HCO_3^-]$, then the change in bicarbonate is greater than the change in anion gap, and there must be an additional non-AG metabolic acidosis present.

6. Summarize your finds by listing the primary disorder + compensation, then all additional (“secondary”) disorders. Examples:
   a. Primary anion gap metabolic acidosis with respiratory compensation
   b. Primary anion gap metabolic acidosis with respiratory compensation plus metabolic alkalosis
   c. Primary respiratory acidosis plus an anion gap metabolic acidosis plus a non-anion gap metabolic acidosis

7. Finally, using the information you know about the clinical situation, match up an etiology for each disorder you have diagnosed. Using the examples from above:
   a. Primary anion gap metabolic acidosis from lactic acidosis with respiratory compensation
   b. Primary anion gap metabolic acidosis from diabetic ketoacidosis with respiratory compensation plus chloride-responsive metabolic alkalosis due to vomiting.
   c. Primary respiratory acidosis from chronic obstructive pulmonary disease plus an anion gap metabolic acidosis from renal failure plus a non-anion gap metabolic acidosis from diarrhea.

IV. Summary

Acid-base balance is controlled immediately by buffers, quickly by changes in ventilation, and then eventually by renal elimination of excess acid or base. Disturbances in hydrogen ion regulation are either primarily respiratory or metabolic, the latter due to variations in production or elimination rates. Clinical distinction usually requires systematic analysis of laboratory data, as well as recognition of an underlying disease process that leads to such abnormalities. Acid-base disorders represent some of the most relevant applications of basic physiology to clinical medicine, and some of the most difficult yet most important to master.

Back to the Emergency Department....
1. In the evaluation of acid-base disorders details as to symptoms, exposures, medication, and status of underlying medical conditions (In this case diabetes and COPD) are essential if the fundamental mechanisms of the observed changes in pH, PCO₂, HCO₃, and anion gap are to be determined. What is his "normal" health state and when and how did it change? What are his baseline laboratory values? What drugs does the patient take, both prescription and OTC? Have any other substances been ingested?

2. The observed respiratory rate and lung auscultation to determine air movement and evidence of pulmonary parenchymal changes are important with regard to PCO₂ and PO₂. The neurological exam provides information as to mental state, muscle strength and irritability, and evidence of focal abnormalities that could be related to substance ingestion and acid-base abnormality consequences. The abdominal exam will help to clarify the etiology of the abdominal pain and the stool guaiac will provide evidence of possible bleeding.

3. To dissect out the potential acid-base responses in this complex patient the first thing to do is to look at each known clinical condition and determine what the anticipated acid-base findings would be for each condition independently.

   a. COPD can be associated with CO₂ retention. This leads to a primary chronic respiratory acidosis with a resultant mild/moderate acidemia. The renal response is the development of a compensatory metabolic alkalosis to maintain a pH as close to 7.4 as possible. An increase in shortness of breath (SOB) may be a symptom of additional airflow restriction accompanied by increased CO₂ retention and a worsening primary respiratory acidosis.

   b. If the SOB is a response to hypoxemia due lung parenchymal disease such as pneumonia than the possibility of a resultant mild/moderate primary metabolic lactic acidosis must be considered. Lactic acid would increase the anion gap. The normal response to a lactic acidosis would be the development of a compensatory respiratory alkalosis, however with the primary driver in this patient a pulmonary disorder this compensation will not be obtained.

   c. The patient has known diabetes and may have developed a primary metabolic acidosis due to ketoacid production. This would cause an increase in the anion gap and normally stimulate the development of compensatory respiratory alkalosis.

   d. The vomiting would result in the loss of stomach acid and also contribute to volume depletion. Both conditions would stimulate the development of a primary metabolic alkalosis. With volume depletion more sodium is reabsorbed in the proximal tubule. The sodium reabsorption is associated with increased HCO₃ reabsorption.

   e. Ingestion of increased doses of salicylates for treatment of the osteoarthritis could, given the total dose, be a cause of an anion gap primary metabolic acidosis.
This should stimulate the development of both a compensatory respiratory alkalosis and through a central effect a primary increase in the respiratory rate.

4. The key laboratory tests are the measurement of pH, PCO₂, HCO₃, O₂ and the anion gap. Additional tests of value would be an electrolyte panel (sodium, potassium, and chloride), measurement of renal function from the blood urea nitrogen (BUN) and serum creatinine, and a salicylate level. The anion gap will further define the presence of unmeasured anions that in this case could be drug, ketoacids, or lactic acid. If additional pulmonary information is required a chest x-ray will help to establish the presence of infiltrates and severity of the underlying COPD.

Once this data is collected, the various formulas that describe the anticipated compensatory responses to the various primary disorders can be applied. It should be anticipated that in a patient with COPD that the extent of respiratory compensation for metabolic acidosis will be compromised. This patient can be expected to have a combination of primary acid-base disorders and as such would be defined as having mixed disorders.

5. Therapeutic interventions are sequenced and will be directed at the various underlying conditions causing the observed acid-base disorders in order of their severity. Treatment of the COPD would be directed at improving airflow and oxygenation with a fall in PCO₂ and improvement in the respiratory acidosis. Correction of an oxygenation problem would lessen the stimulus for the metabolic lactic acidosis. Correction of GI disturbance with an end to the vomiting and supplemental volume replacement will correct the metabolic alkalosis. Depending on the salicylate level, and when the drug was taken, the patient can be treated with stomach lavage and in more severe cases hemodialysis. Bicarbonate infusion is also provided.

As each abnormality is addressed the subsequent effect on compensatory mechanisms must be anticipated. We must be cautious to avoid over correction through the use of mechanical ventilation, dialysis, or bicarbonate infusion. Remember the goal is to get the pH back as close to normal 7.4 as possible!

6. The presence of long-term diuretic therapy is usually associated with the development of a chloride sensitive metabolic alkalosis and total body potassium depletion. This underlying state may mask the severity of a new primary metabolic acidosis or worsening the presentation of an additional primary metabolic alkalosis. It may also complicate the changes noted in serum potassium with certain metabolic conditions.
Practice questions (and answers)

1. A 30 year old male is found down and unresponsive. His initial arterial blood gas findings reveal the following: pH=7.10, pCO2=22, pO2=100 and his serum chemistries reveal a sodium of 140, a potassium of 4, a chloride of 100 and a bicarbonate of 10. What is his primary acid-base disorder?
   a. Metabolic alkalosis
   b. Metabolic acidosis
   c. Respiratory alkalosis
   d. Respiratory acidosis
   e. Wide (elevated) anion gap metabolic acidosis

2. What is his secondary acid-base disorder?
   a. Metabolic alkalosis
   b. Metabolic acidosis
   c. Respiratory alkalosis
   d. Respiratory acidosis
   e. No secondary disorder

3. Which two organs cause non-anion gap metabolic acidosis?
   a. Kidney and lungs
   b. Kidney and GI tract
   c. Kidney and heart
   d. Kidney and adrenals

4. Which two organs cause respiratory acid-base disturbances?
   a. Kidney and lungs
   b. Lungs and heart
   c. Lungs and GI tract
   d. Lungs and brain

5. If the $\Delta$AG equals the $\Delta$[HCO3-] then
   a. There is no acid-base disturbance.
   b. There is no metabolic disturbance.
   c. The metabolic compensation is chronic.
   d. The change in bicarbonate concentration can be entirely explained by the change in anion gap.
Answers:

1. This patient has an acidosis (pH below normal) which is metabolic in nature (low pCO2; if this were respiratory acidosis the pH would be high). He also has an elevated anion gap (140-110=30). The answer is e. wide anion gap metabolic acidosis.

2. To determine if there is a secondary disorder, you need to address the “other” system (If metabolic is primary disorder, is the respiratory compensation appropriate? If respiratory is primary disorder, is the metabolic compensation appropriate?). In this case the patient has a primary disorder of metabolic acidosis so one needs to address the appropriateness of the respiratory response. Fortunately, there is an equation to help with metabolic acidosis—Winters formula. Using this formula, expected pCO2=1.5 (bicarb) +8±2; in this patient 15+8±2 or 21-25. Here the pCO2 is 22 so the compensation is appropriate. Finally, because there is a metabolic acidosis, one must compare the ∆AG to the Δ[HCO3-]. The ∆AG is 30-12 =18, while the Δ[HCO3-] is 24-10 = 14. Since the ∆AG is greater, there is an additional metabolic alkalosis which is keeping the bicarbonate higher than would be expected just from the ∆AG.

3. (b) Almost every etiology for NAGMA is due to a renal or GI process (see Table 1). One notable exception is that a NAGMA can be cause by i.v. infusion of large amounts of normal saline.

4. (d) The principal causes of respiratory disturbances are due to mechanical or anatomical pulmonary problems or to abnormalities in the central respiratory drive.

5. (d) The change in bicarbonate is due to the change in the change in anion gap, and we don’t have to look for another metabolic process to explain it.
ICR 2013-2014 Acid-Base Case Studies

In each ICR small group session, your preceptor will facilitate a discussion of key clinical aspects during the session. The goals of each and every ICR small group are to develop clinical reasoning skills as the fundamental building blocks of clinical medicine. These goals are achieved via the following objectives independent of the content specific objectives:

1) Illustrate major diagnostic entities (common and/or serious) for the topic.
2) Describe typical patterns of presentation for these diagnostic entities (classic or typical patterns)
3) Construct prioritized problem lists
4) Create a relevant differential diagnosis
5) Demonstrate clinical reasoning by justifying the differential diagnosis using key clinical information or decision points towards establishing the diagnosis
6) Reinforce use of proper medical terminology and pathophysiology germane to each case

Every ICR small group is intended to be a “low-stakes” learning environment where active participation is encouraged and supported with content and context-specific preceptor feedback. Preceptors will assess your clinical reasoning through active listening as you discuss problem lists, differentials, and management aspects for each clinical exercise. Preceptors will use a number of techniques to encourage participation so they can observe and assess your clinical reasoning skills. Preceptors also model clinical reasoning in their clinical approach to the exercise.

*It is worth mentioning again -- Without active participation, preceptors will not be able to assess your clinical reasoning skills. For this reason, active participation is required!*

**Lastly, your feedback for the course is valuable and enables us to continually improve!**
PROBLEM 1
For each of the following clinical situations, give the following:
i) the potential primary acid-base disorder (metabolic vs. respiratory, acidosis vs. alkalosis, acute vs. chronic). For metabolic acidosis, specify whether the anion-gap would be normal or elevated. State the direction of change in pH, pCO2, and serum bicarbonate caused by the disorder.
ii) a brief differential diagnosis underlying the proposed primary acid-base disorder
iii) the expected type of compensatory process
iv) the types of possible additional (“tertiary”) disorders. Present the same details as for part (i).

a) a 67 y.o woman with chronic obstructive pulmonary disease (COPD) is in her usual state of health
b) a 67 y.o woman with COPD is started on a thiazide diuretic for hypertension
c) a 22 y.o. woman who is 29 weeks pregnant is in good health
d) a 12 y.o. girl presents with nausea and vomiting after several weeks of polyuria and a 5-kg weight loss
e) a 45 y.o. man with a history of alcohol abuse is found unresponsive in a garage
f) an 42 y.o. man presents with 3 days of vomiting
g) a 37 y.o. female is brought to the emergency department with acute onset of right-sided pleuritic chest pain and arterial oxygen saturation of 89%
PROBLEM 2
For each set of lab values presented, determine:
i) the primary acid-base disorder
ii) if the actual compensatory response equals that expected
iii) the anion-gap and if elevated, the delta-delta
iv) if there are additional processes
v) if the lab data is consistent with any of the situations in Question 1

a)

<table>
<thead>
<tr>
<th>ABG</th>
<th>Electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
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<td>Na</td>
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<td>K</td>
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<td>Cl</td>
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<tr>
<td>HCO₃</td>
<td>11</td>
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d)

<table>
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<td>Cl</td>
<td>110</td>
</tr>
<tr>
<td>HCO₃</td>
<td>11</td>
</tr>
</tbody>
</table>
PROBLEM 3

A 77 year old man is brought into the emergency room by a concerned family member because he has been having “the dwindles”. He notes a lack of energy and appetite for a week along with a 6-lb weight loss and intermittent vomiting over the past three days. His medical history is significant for hypertension for which he takes a diuretic, and a 150 pack-year smoking history.

On exam he is a lethargic-appearing white male who is alert and oriented. His vital signs: height 69 inches, weight 130 lbs, T 99.1 F, BP 91/61, pulse 109, RR 28/min, oxygen saturation 92% breathing room air. The skin has decreased turgor. Cardiopulmonary exam is significant for tachycardia and a prolonged expiratory phase with scattered faint wheezing. ECG is normal.

Laboratories:

<table>
<thead>
<tr>
<th>Basic metabolic profile</th>
<th>Arterial blood gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na = 134 mEq/L</td>
<td>pH=7.20</td>
</tr>
<tr>
<td>K = 3.7 mEq/L</td>
<td>pCO₂=45</td>
</tr>
<tr>
<td>Cl = 88 mEq/L</td>
<td>PO₂= 65</td>
</tr>
<tr>
<td>HCO₃ = 17 mEq/L</td>
<td></td>
</tr>
<tr>
<td>BUN = 44 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Cr = 1.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Glucose = 87 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Questions (this is a complicated case, so be sure to go through all the steps):

1. Construct a problem list for this patient’s presentation (symptoms, signs, and laboratory abnormalities).

2. What is his primary acid-base disorder? Is there appropriate compensation or does one or more secondary disorder exist? If a secondary disorder exists, what is/are the disorder(s)?

3. List the causes of his primary acid-base disorder? What do you think is the cause of his disorder and what laboratories would you obtain to confirm this? List potential causes of any secondary disorders.

4. What is the pathogenesis of his low bicarbonate concentration?

5. What therapeutic measures would you consider at this time?
INTRODUCTION TO CLINICAL REASONING:
NEUROLOGY

Carl H. Gunderson, MD
David M. Bartoszek, MD

INTRODUCTION: In comparison with many other specialties, neurologic diagnosis depends very heavily on the practitioner’s ability to localize a patient’s problem within the nervous system. In most patients this can be determined by history and physical examination. In other patients (like headache) the diagnosis must rely on history alone. Although imaging has gone far to confirm anatomic lesions, it is far more effective if the clinician can direct the attention of the radiologist to a specific area of interest. In this module we will present two closely related tools to assist in developing a neurologic diagnosis. We will begin by dealing directly with the clinical information that the patient provides and then move on to more advanced analysis based on the patient’s chief complaint.

OBJECTIVES

A. Provide a working algorithm for neurological diagnosis based on the history and physical exam.

B. Provide diagnostic schemas for common chief complaints presented by patients with neurological illnesses.

C. At the end of the neurological segment, students should be able to:
   1. Identify from a vignette that a patient has a neurological disorder
   2. Correctly identify the presenting syndrome.
   3. List most likely cause of that syndrome.

Patient 1:

A 72-year-old man presents to the emergency room complaining of weakness in his left face and arm. He reports that his symptoms began about an hour ago and have been getting worse. A review of his medical record reveals that he is being followed regularly for an elevated cholesterol, mild hypertension and glucose intolerance.

Physical Examination reveals a blood pressure of 145/80 mmHg and pulse of 84. Respirations appear normal. There is a soft bruit over his right carotid artery. Pulse is irregularly irregular, but no cardiac murmurs are appreciated.

The remainder of the significant findings is limited to the nervous system. His speech is slurred and difficult to understand. Visual fields and extra ocular movements are normal. When he smiles, his face is drawn to the right with decreased movement in the left lower face. Forehead wrinkling is symmetrical.
Tongue and palate movements appear symmetrical. His left arm is severely weak including all muscle groups. He also has mild weakness of the left foot. Cutaneous modalities of sensation (light touch, temperature, and pain sensation) are diminished in the left face and arm. Reflexes in the left arm are exaggerated and there is a Babinski sign on the left.

**Patient 2:**

An 18-year-old Air Force recruit presents to the emergency room on a Monday morning referred from the health clinic complaining that his feet are weak and tingling. He first noticed the tingling sensation on Friday afternoon after a road march. He thought it would go away so he proceeded with his weekend plans which included a drinking party on Saturday night. Sunday morning he started tripping over things and this morning he felt that his feet were getting weak. Review of his health record revealed that he has been in excellent health and passed all physical exams and received all of his immunizations.

Physical examination reveals a muscular appearing man with normal vital signs. The patient gave a coherent detailed history so the mental status exam was omitted. Cranial nerve examination was likewise normal. Strength was normal at the shoulders, elbows, hips and knees. It is 4- in dorsiflexion of both ankles, and 4- for movements of the toes. Adduction and opposition of the thumb was 4- as was abduction of the 5th digit. Other fine movements of the fingers were also weak. There was mild diminution of vibration, position, touch and pinprick sensation over both feet up to the ankles, although pain and pinprick are better preserved. All deep tendon reflexes were absent. Babinski signs were absent. Romberg sign is present.

Read the next section for the tools you need to solve these patient problems. Answers appear under “something doesn’t work right anymore.”

**I. TOOLS FOR IDENTIFYING NEUROLOGICAL ABNORMALITIES**

A. The most powerful tool is a good history.

1. The physician must first determine the exact nature of the complaint.
   a. The patient’s use of words to describe a symptom does not always coincide with the physician’s meaning of the same symptom.
   b. Good examples are dizziness and numbness. Patients will often use “dizziness” to refer to vertigo, lightheadedness, or even a gait disturbance.
   c. In addition to loss of sensation or tingling, “numbness” is often used to describe weakness, coldness, or other non-specific sensations. It is best to ask the patient, “What do you mean by ....”
d. Although in some cases risk factors may suggest a diagnostic possibility, they do not make a diagnosis and can be deceiving if relied on too heavily in evaluating a patient with a neurologic disorder. For example, an elderly patient with primary brain tumor is likely to have several risk factors for stroke.

2. An accurate description of the speed with which symptoms develop as well as the way that they evolve is essential.

3. Determine whether this a single event or one of many, and if many, are the events all the same?

4. Patients with some common neurological problems do not display physical findings at the time they arrive at the emergency room or the provider’s office. These include many of the headache, seizure, and dizzy disorders. In these cases the history may be the only thing that the provider has to go on. It is convenient to lump these together under the heading of “spells.”

B. The Neurological Examination

1. No one has enough time to do everything that can be performed on a neurologic examination. Performing a “Complete Neurologic Examination” is a clinical oxymoron. The provider should learn to perform a “targeted exam” based on the history. It is usually valuable to perform a brief screening exam to ensure that some other part of the nervous system is not malfunctioning.

Clinical Pearl: A skillful examiner can perform a fairly good screening examination by observing the patient while taking the history. If the patient can give a good history complete with dates, providing answers to the provider’s questions, and using language appropriately it is unlikely that his mini-mental status exam will be abnormal. Similarly watching spontaneous movements of the eyes and face may remove the necessity for a more detailed cranial nerve exam. Finally, if the patient is freely moving all extremities and has no complaints of weakness or sensory loss a great deal of motor and sensory testing is unlikely to be productive. Testing rapid alternating movements, finger to nose testing, and deep tendon reflexes may be all the formal testing needed.

2. Any abnormality in the neurologic exam confirms that some area of the nervous system is malfunctioning.

3. The first decision point in localization is determining whether the disorder is attacking the central (brain and spinal cord (CNS)) or the peripheral nervous system (nerves entering or leaving the spinal cord and brain stem (PNS)).
4. Next in importance is determining whether the disorder is affecting only a portion of the CNS or PNS or if it is affecting entire system or multiple systems.

5. Within the CNS, diffuse disorders often appear to affect only one structure (i.e. the substantia nigra in Parkinson’s disease), although on both sides of the brain. As the disease progresses, it’s truly diffuse nature will become apparent.

C. From the information obtained during the history and physical, the provider should be able to recognize one of the dozen or so syndromes produced by disorders of the nervous system. Experienced clinicians use algorithms of this sort, often subconsciously, to quickly arrive at a working diagnosis. As an additional aid, we have proposed a name for each syndrome suggesting the most common disorders producing it. Only three facts must be established in order to use this approach.

1. How rapidly did the complaint develop? For example:
   a. Epileptic seizures can fully develop in milliseconds.
   b. Disorders like stroke develop rapidly over a period of minutes to hours.
   c. Slowly developing abnormalities like those produced by tumors and degenerative disorders require days to weeks and even years to fully develop.

2. Does the disorder affect the central or peripheral nervous system? Trauma and some toxic disorders are among the few that can affect both at the same time.

3. Is the disorder focal or diffuse? In addition, the physician should be able to determine roughly which part of the nervous system is involved.

II. SYNDROMES AFFECTING THE CENTRAL NERVOUS SYSTEM

A. Stroke Syndrome: These are rapidly developing focal disorders of the CNS. Nearly all of them are caused by either occlusion of an artery producing ischemic stroke or the rupture of an artery producing a hematoma or subarachnoid hemorrhage. Acute subarachnoid hemorrhages account for only about 3% of strokes and produce an encephalopathy syndrome that can begin rapidly (see below) instead of the more common focal deficits produced by infarctions and hematomas.

B. Tumor Syndrome: These more slowly developing focal disorders of the CNS are caused by processes such primary neoplasms, metastatic neoplasms,
granulomas, abscesses or demyelinating plaques associated with multiple sclerosis.

NOTE: While multiple sclerosis is ultimately a diffuse disorder affecting many parts of the brain, initial and early attacks are usually highly focal CNS disorders. They usually take days to reach days their full severity. The plaque behaves like a more rapidly developing mass lesion. Either CT or MRI scanning can easily determine the identity.

C.  **Degenerative Syndromes**: These are very slowly developing CNS disorders which in time may be truly generalized but affect primarily one system on presentation. However, their bilateral presentation at onset differentiates them from the tumor syndrome. They may present as cerebral, basal ganglion, cerebellar, brain stem or spinal cord disorders.

D.  **Encephalopathy/delirium Syndrome**: This syndrome features the evolution of symptoms generalized CNS dysfunction over hours. It is usually caused by infection, metabolic disorders, or toxins including alcohol and prescription medications.

E.  **Spells**: These are episodes of altered behavior, sensation, or consciousness which leave no abnormalities on neurologic exam. The identification of the nature of the episode and often its cause must be determined by history alone or by examination techniques that reproduce the symptoms. These include the epilepsies, headaches, and some of the dizzy presentations.

### III. SYNDROMES AFFECTING THE PERIPHERAL NERVOUS SYSTEM

A.  **The Neuropathy Syndrome**: This is a large group of slowly progressive disorders of the PNS. Most are diffuse and produce a mixture of motor and sensory deficits, although some can be purely motor or sensory. Small fibers that convey sensory information about pain and temperature perception are often the first affected. There are some multifocal types. Guillain-Barré syndrome is special in that it usually develops over a few days; much more rapidly than any of the other peripheral neuropathies.

C.  **Disorders of nerve roots, single nerves, and plexi**: These are usually caused by physical injury of some sort. They may develop suddenly as is often the case with a herniated disk or very slowly as with the carpal tunnel syndrome.

D.  **The Myopathies**: These disorders are usually slow to develop, exhibit proximal weakness (except for the myotonic varieties and inclusion body myositis) and are not associated with any sensory loss. This last feature is the easiest criteria to separate them from the peripheral neuropathies which usually have at least some features of sensory loss.
IV. APPLYING THE SYNDROMES to CHIEF COMPLAINTS SUGGESTING A DISORDER OF THE NERVOUS SYSTEM

Overview

Schemas are decision trees or algorithms (ICR Topic 1), which provide a useful diagnostic tool or approach for clinicians. This section on clinical reasoning reviews schemas to help you establish the differential diagnosis of common chief complaints and syndromes in neurology. It is followed by a syndrome approach to recognizing patterns of neurologic disorders. Further, this section provides video prototypes seen with many of the diagnoses in each schema to help you build a picture of what each of the diagnoses looks like (i.e. a basic illness script). Additional case studies are available in Blumenfeld and are referenced in the text. Additional details on the chief complaints may be found in “Introduction to Neurological Diagnosis” which closely follows this review.

A. “Something doesn’t move right” (Schema #1). This applies to all voluntary movements controlled directly by the central or peripheral nervous system. Anatomy review for the voluntary movement disorders that produce weakness is presented below.

**Anatomy Review, Motor Systems:** Making skillful voluntary movements requires the interaction of four parts of the nervous system and support from several others.
The upper motor neuron consists of neurons in the cerebral motor strip which descend to control cranial nerves, brain stem reflex centers, and anterior horn cells in the spinal cord. This pathway never leaves the central nervous system. Everywhere in the brain (including the brainstem) it remains on the side of origin; while everywhere in the spinal cord it is on the side of its innervation due to the fibers crossing at the junction of the brainstem and spinal cord. Lesions in the system produce weakness, hyperreflexia, and release of “abnormal” reflexes such as the Babinski sign. Spasticity is often a late development.

The motor unit (lower motor neuron) includes the nuclei in the brainstem that innervate skeletal muscle; and the anterior horn cells of the spinal cord, their axons, the synapse on muscle fibers, and the muscle fibers themselves. Disorders of the system produce weakness, decreased or absence of all reflexes, and are usually accompanied by sensory findings.

The cerebellum and basal ganglia are supporting structures. Their disorders produce either clumsiness or unwanted movements. Lesions in these structures never produce weakness. Weakness can be produced only by disorders of the upper and lower motor neurons.

1. Patient #1: This is clearly a very rapidly developing problem. The distribution of weakness in his face and arm on the same side strongly suggest a central nervous system cause (upper motor neuron). Since only a small part of the body is weak; this must be a highly focal CNS lesion. A peripheral nerve disorder would be very unlikely to strike simultaneously in two different, widely separated locations. Cells in the cerebral cortex controlling face and arm movements are both irrigated by the middle cerebral artery. Thus, before even thinking about ordering a scan the practitioner should feel secure that he’s dealing with a stroke syndrome. The exaggerated reflexes and Babinski sign on the neurologic exam confirmed these conclusions. Although the distribution, the risk factors, and statistics would suggest that this is an infarction, a CT scan (or an MRI) is needed to exclude the possibility of a hematoma.

2. Patient #2: Evaluating the initial history of bilateral weakness and sensory loss in the patient’s feet would suggest either a spinal cord lesion or a peripheral neuropathy. Notice that in this focused examination the mental status exam and the cranial nerve exam were omitted. For comparison, strength was examined in the shoulders and arms. Abnormalities were found that were not suggested in the history. In contrast to Patient #1, all deep tendon reflexes were abolished and Babinski’s sign was absent. These features indicate a PNS process and not a spinal cord disease. The speed of development would strongly suggest that this young patient has a Guillain-Barré syndrome and is in urgent need of either plasmapheresis or IV IG.

3. Patients #1 and #2 illustrate that weakness can result either a disorder of the central or peripheral nervous system. Whenever weakness is present, the only possible anatomic choices are an upper motor neuron or motor unit disorder.
Distinguishing between these alternatives is relatively easy if the pattern of involvement can be determined. Central nervous system disorders are usually hemiparetic (weakness on one side of the body) or paraparetic (weakness in both legs) in pattern. Peripheral nervous system disorders generally are distal and may appear in all 4 extremities as well as cranial nerves.

**Patient #3:**

This 63-year-old retired carpenter has found it increasingly difficult to do any wood working. He has no immediate explanation but has noticed that when he sitting quietly his hands shake. Examination reveals no weakness or sensory loss. However, both hands display slow, rhythmic “pill rolling” movements. Rigidity can be appreciated at both wrists and his gait is slow and halting.

4. Patient #3 is another example of “something doesn’t move right”. However he does not complain of weakness but rather clumsiness and unwanted movements. These symptoms are usually caused by abnormalities of either the cerebellum and its connections or the basal ganglia and their supporting structures. The tremor usually allows for differentiation. If it is slow and at rest it is probably originating in malfunction of the basal ganglia or one of their supporting structures such as the substantia nigra. Cerebellar movement disorders hand tend to be worse during voluntary movement and are best seen on finger to nose and heel to shin testing.
B. **“Something doesn’t feel right” (Schema #2)**. Patients with sensory disorders usually complain of either a loss of sensation (hypoesthesia) or abnormal sensations (paresthesias). These may be summarized as “the numbs and the tingles”.

**Anatomy Review, Sensory Systems:** The somatic sensory system carries information to the brain from the skin, muscles, and joints. Nearly all peripheral nerves have their cell bodies in either the dorsal root ganglia or the named peripheral sensory ganglia of the cranial nerves. Axons and their myelin sheaths can be classified as either large or small fibers.

The “Large fibers” are heavily myelinated, fast conducting axons that convey vibratory and position sense as well as the afferent limb of the reflex arc. In the central nervous system, these fibers travel in the posterior columns of the spinal cord and the medial lemniscus in the brainstem. The “Small fibers” are slower conducting, thinly myelinated and unmyelinated axons that convey pain and temperature perception. They synapse upon entering the spinal cord and cross to the contralateral lateral spinothalamic tract. Secondary axons carry this information to the cortex in the lateral spinothalamic tracts.

**Patient #4**

Mr. Jones is a 65-year-old man who has been recently diagnosed as having type II diabetes. He is always been a consumer of large amounts of alcohol on a daily basis and considers restriction of this activity to be his chief disability. However, on this visit he complains that he has trouble with a numb feeling in his toes that has been progressing over the last month. On examination, neurologic findings are limited to his feet where he has marked diminution of pain sensation in his toes and somewhat less on the dorsum of his feet. Position and vibration sense in his toes are diminished to a lesser degree. Ankle jerks and Babinski signs are absent.

1. These complaints are often associated with “something doesn’t work right” and they may be due to disorders of either the central or the peripheral nervous system. When due to central nervous system disorders they tend to be either on one side of the body (including face) or symmetrically below a spinal cord level. When due to peripheral nervous system disorders they generally follow one of 2 different patterns. Sensory complaints in diffuse processes are present distally in the limbs. In focal processes the sensory complaints are present in the distribution of the nerve, nerve root, or plexus affected. It is often easier to localize these accurately by the applying information from the accompanying motor deficit.

2. Examination of the patient with sensory complaints should include 4 of the 5 sensory modalities: position, vibration, pain, and touch (temperatures a modality that more difficult to test and redundant if pain is been tested). Spinal cord lesions are unique in that they may produce position and vibration loss on one side while pain and touch are diminished on the other. As one may suppose, these complaints seldom accompany lesions in the cerebellar or basal ganglion systems. Some peripheral nerve disorders will selectively attack the large fiber rapid conducting heavily myelinated axons (Guillain-Barré) while others will selectively attack poorly myelinated fibers (alcohol and diabetic neuropathies).
3. Patient 4 illustrates these features. With the history of both type II diabetes and alcohol abuse it may be impossible to tell which of these is injuring his small diameter sensory fibers more severely. The absence of deep tendon reflexes and the ankles could mask a latent hyperreflexia by injuring the sensory limb of the reflex arc if the patient had spinal cord disease. This demonstrates the value of the Babinski sign for this would be not affected and is present in a spinal cord process.

C. “Something is wrong with my vision” (Schema #3). The most common visual disorders are related to the lens (loss of accommodation or cataracts) and are of interest to the ophthalmologist.

**Anatomy Review, Visual Complaints, Visual Afferent System:** It is useful to recognize that the cell bodies for the optic nerves reside in the retina and are actually part of the central nervous system. Therefore, the optic nerves are affected by central nervous system disorders rather than peripheral nerve disorders. Each retina sees objects in all visual fields and the optic nerve from each eye contains information from all visual fields. The visual pathways behind the retina are so constructed that left visual fields are appreciated by the right occipital lobe and vice versa. The fibers from the nasal side of the retina from each eye cross in the optic chiasm. Thus in the pathways behind the chiasm, information from the nasal side of the left retina and the temporal side of the right retina are carried together to the lateral geniculate body (part of the metathalamus) and from there to the occipital cortex. Homonymous hemianopsias result from any lesion in the visual pathway behind the chiasm. Using our algorithm, the sudden onset of a right homonymous hemianopsia (loss in the right temporal and left nasal field) would be a stroke syndrome where the more gradual development might be caused by a tumor or multiple sclerosis.
Patient #5

Ms. Jones is a 26-year-old married woman with three children who was good in good health until about three days ago when vision in her right eye began to blur and she noticed some discomfort on extraocular movement. She has not noticed diplopia nor has she noted any other neurologic deficits. Examination reveals pupils of equal size. However, when the light is shined into the left eye both pupils constrict briskly but when a light is shined in the right eye both pupils dilate.

Patient #6

Mrs. Smith is a 56-year-old woman who awoke this morning complaining of double vision. The double vision went away when she closed either one of her eyes. On examination it was evident that the left eye was deviated inward. On looking to the left the left eye did not deviate while the right eye turned inward normally. In this position the patient complained of severe double vision. On looking to the right the diplopia disappeared.

1. Vascular occlusion of the ophthalmic artery and its branches either produce complete blindness or loss of either the upper or lower fields of the retina in one eye. Gradual loss of macular vision (central scotoma) is seen in macular degeneration. Acute central scotoma is more often caused by optic neuritis which is a focal central nervous system demyelinating disorder. About half of all patients with optic neuritis go on to develop multiple sclerosis.

2. The development of either right or left field loss (homonymous hemianopsia) points to a lesion behind the optic chiasm either in the optic tracts or in the occipital lobes. If rapid in development these are caused by strokes. More gradual development is most often caused by multiple sclerosis but can be caused by other kinds of tumors.

3. Patient #5’s loss of vision is due to injury to the optic nerve. The physical exam confirms this. When light is shined into the good eye the pupils react normally, both pupils constricting. When the light is transferred to the symptomatic eye, both pupils dilate. This is called an afferent pupillary defect (APD) or a Marcus Gunn pupil. The mechanism for this response is that when the light appears in the good eye the pupillary reflex centers receive the full impact. When the light is shined in the symptomatic eye the amount of visual information is reduced because of injury to the optic nerve with resultant pupillary dilatation. This is usually caused by optic neuritis.

4. Patient #6 illustrates a problem within the visual efferent system. This system is concerned with ensuring that both eyes are aligned (so that images fall at exactly the same areas in each retina), stay fixated on an object when with the patient or the object is moving, or redirect gaze to move to another position. Acquired diplopia or double vision (Patient #6) is an example of the malfunction of this system. It is usually binocular and due to some disorder of the extraocular muscles, the nerves that supply them, or their brainstem nuclei and their brainstem connections. The 3 cranial nerves that control eye movements may be individually injured. This is most common when increased volume on one side of the cerebrum (such as a hematoma) forces the temporal lobe to herniate downward through the incisura in the tentorium cerebelli thus stretching the 3rd nerve producing dilatation of the ipsilateral pupil and restriction of eye movements controlled by the 3rd nerve. Uncommonly diabetes or other generalized disorder may cause isolated cranial nerve palsy. Brainstem lesions from stroke or
multiple sclerosis may injure cranial nerve nuclei or their connections (such as the medial longitudinal fasciculus producing intra-nuclear ophthalmoplegia).

D. “I have headaches” (Schema #4 & #5):

**Patient #7:** A mother and her 16 year old daughter are seen in the Adolescent Clinic. The daughter complains that for the last year she has been having headaches nearly every month associated with her menstrual periods. These headaches are very severe, pounding in quality, and last for several hours. They make her nauseated and she frequently vomits during a headache. The mother had similar headaches when she was younger but always had improvement with over-the-counter analgesics. These medications have not helped her daughter. Physical examination is normal.

**Patient #8:** 36 year old accountant, a married dependent of one of the Nursing Officers, complains of headaches as the tax season is ending. These seem to happen every year and they are starting to interfere with his work. They usually start late in the day and creep up on him. They are a tight feeling in the back of his head. The neurologic examination is normal.

1. Analyzing the type of headache patient begins with determining whether the headache is recurrent or a new onset. Patients #7 and #8 are examples of the two most common forms of recurring headache. Patients usually present to the provider during inter-headache periods and without any abnormal neurologic findings and thus may
be included in our category of “spells.” There are a number of red flags that should alert the provider that these may not be simply benign recurrent headaches (benign in the sense that they are rarely fatal, but may cause the patient’s days of agony). Headaches associated with subarachnoid hemorrhage, meningitis, or viral meningitis will be described differently than the more stereotyped recurrent headaches. Subarachnoid hemorrhage may awaken patients from sleep or may develop so fast as to be called a “thunderclap headache.” Any alteration in the neurologic examination, including the Glasgow coma scale, demands more aggressive evaluation. The same may be said of papilledema or other signs suggesting increased intracranial pressure such as recurrent morning headaches that disappear throughout the day.

2 Both of these headache examples share the repetitive quality of the headaches and a normal neurologic examination. Patient #7 gives a classic migraine history. The most important features are the unilateral headache, the severity of the headache, and its repetitive pattern. Most of the other features such as the photophobia, nausea, vomiting, and the lack of preceding aura are useful but not conclusive.

3 Patient #8 reports none of the characteristics of migraine headache. The headache generally develops slowly, the pain is not as severe, and tends to localize at the back of the head. Headaches can often be related to specific stressors although the identification of the triggers is not necessary for diagnosis. This description is typical of tension-type headache.

4 The 3rd kind of repetitive headache is the cluster headache. These tend to occur later in life and are somewhat more common among men than women. Like migraine the headaches develop very rapidly and are one sided. As opposed to migraine, cluster headaches seldom last more than an hour. Patients characteristically display autonomic dysfunction such as lacrimation, nasal discharge or facial flushing on the side of the headache. As the name suggests, these headaches tend to occur in clusters lasting a few weeks or months but may recur again at a later time.

5 Behavioral headaches are those related to specific behaviors such as eating something cold (ice cream headache) or consuming processed meats (hotdog headache). Patients will frequently recognize the specific stressor and alter their behavior without seeking medical attention.
**Patient #9:** A 26-year-old woman is brought to the emergency room by her husband at 3 o’clock in the morning. He relates that she awoke about a half an hour ago complaining of a terribly severe headache all over her head. He called the ambulance and she was brought to your emergency room. Her Glasgow coma scale was 12 but there were no focal neurologic findings beyond photophobia and a stiff neck.

Patient #9 is an example of a non-recurrent headache. It lacks the repetitive pattern of the headaches described above. Furthermore, one cannot include this among the “spells category” because of the Glasgow coma scale. Such alterations of consciousness always imply a diffuse malfunction of the cerebral cortex. This makes it an acute encephalopathy. There can be a broad differential diagnosis and should include subarachnoid hemorrhage, viral encephalopathy, bacterial meningitis, as well as a host of metabolic and toxic disorders.

**SCHEMA #5:**

![Diagram](image-url)
E. “I have these funny spells” (Schema #6): This involves a number of experiences that the patient may have had including epileptic seizures, presyncope and syncope, and a variety of psychogenic experiences.

**Patient #10:** A 38-year-old woman, previously in good health, was found by her husband to be convulsing on the kitchen floor. After a few seconds she stopped all motor activity and lay quietly without breathing for several seconds until respirations resumed. An ambulance was called and she was brought to the hospital emergency room. On admission she appeared dazed and confused and her left arm appeared weak (Todd’s paralysis). After a few minutes she regained full motor and intellectual function. When questioned she remembered several episodes over the last several weeks when she would encounter an unexplainable unpleasant odor for 3 or 4 minutes.

1. Epilepsy is of the greatest interest to the neurologist.
   a. Seizure disorders may be either partial (abnormal neuronal discharge is arising from a small part of the brain) or generalized from the start (abnormal neuronal discharge involved the entire cortical surface). In adults, generalized seizures are often secondary to partial seizures that have spread.
   b. It is customary to think of partial seizures as being either “simple” or “complex.” Simple partial seizures may involve abnormal movements, cutaneous sensations, visual disturbances, bad smells or tastes, or even changes in mood or feelings. There is no alteration of consciousness and patients can often describe what occurred during the attack.
   c. Complex partial seizures most often arise from the temporal lobe and have an altered awareness with stereotyped behaviors called automatisms (lip smacking or eye blinking). The patient is confused for a period of time after the seizure is finished. This is called a post-ictal state.

2. Patients with presyncope and syncope will often be able to relate a feeling of lightheadedness or dizziness before the loss of consciousness. Syncope is a diffuse cerebral anoxic disorder and may trigger myoclonic jerks that resemble seizure activity (and probably are). These episodes are often described as convulsive syncope.

3. A detailed history concerning symptoms present at the very onset of the event, a collateral history describing precise details about behavior during the spell, duration of the spell, and symptoms present at the conclusion of the spell (such as confusion or weakness) is critical to making an accurate diagnosis.

   **SCHEMA #6:**
F. “I’m dizzy” (schema #7): This is among the most challenging complaints to deal with. The patient will frequently use this term to describe several common conditions.

Anatomy review: The vestibular apparatuses and the nerves that connect them to the brainstem are unique among peripheral nervous system structures in that they are constantly bombarding the brainstem with electrical discharges. These discharges compensate for head movements and are important in maintaining visual fixation. Under normal circumstances the discharges from the left ear and the right ear balance each other. The left ear tries to push the eyes to the right while the right ear tries to push the eyes to the left. These not only affect eye movements but also movements of the trunk and limbs if the eyes are closed (past pointing and the step tests).

Diseases or injuries to one of the vestibular systems will cause an abnormal increase or decrease in the input to the brainstem from the affected vestibular system. When there is a decrease in vestibular input the eyes will tend to drift towards the sick ear. The brain tries to correct this with opposing fast saccadic jerks producing the familiar drift and jerk nystagmus. Although it is traditional to name the direction of nystagmus by the rapid component the pathologic movement is usually the slow drift. This is the direction in which past pointing and step testing will be generated. The patient may complain that either they are spinning or the room is spinning around them.

Patient #11: A 34-year-old internist complains of feeling dizzy and nauseated. He describes the dizziness as a persistent sensation of spinning toward the left. This all started shortly after morning rounds and has been getting worse over the last three hours. He has vomited twice. On examination, he appears acutely ill. On looking to the right he has right beating nystagmus (eyes
drift left and then jerk back to the right) which goes away on looking to the left. He past points
to the left and when walking veers to the left. The remainder of the exam is normal.

1. True vertigo is a common complaint and may present in several patterns.
   a. The most common is benign paroxysmal positional vertigo (BPPV). Its
      historical signature is a complaint of frequent episodes of vertigo when
      changing position in bed. Typically these last for only seconds and are
      seldom long enough to produce nausea or emesis. The diagnosis can be
      confirmed by an exam maneuver called the Dix Hallpike test in most
      patients. It is caused by loose material in the vestibular apparatus and can
      often be successfully treated with positional exercises.
   b. Meniere’s disease (endolymphatic hydrops) is also intermittent but as
      opposed to BPPV it does not have a positional quality, the attacks last
      longer, and are often associated with tinnitus. Over time the patient will
      experience hearing loss in the affected ear.
   c. Vestibular neuronitis and acute labyrinthitis differ from both BPPV and
      Ménière’s disease in that they develop on over several hours and patients
      may be sick for days. Although there is some debate over the pathology,
      conventionally the term vestibular neuronitis is used when there is no
      hearing loss and labyrinthitis when hearing loss is present.
   d. Patient #11 is a good example of vestibular neuronitis. All of the features
      of the physical exam can be traced to the peripheral nerve or the labyrinth
      and thus, fall within the peripheral nervous system. There are no findings
      to suggest an alternate localization within the brainstem. Vestibular
      neuronitis falls within the group of mononeuropathies. There is MRI
      evidence that at least in some cases there is inflammation in the nerve.
   e. Two less common disorders need to be mentioned. First, the Ramsay
      Hunt syndrome (herpes zoster of the geniculate ganglion), which can be
      distinguished by pain in the ear followed by a rash in the auditory canal. In
      addition, after trauma patients may develop endolymphatic fistula.
   f. All of the above are basically peripheral nervous system problems.
      However dizziness, and especially vertigo, can also be caused by focal
      disorders of the brain stem including strokes and multiple sclerosis. A
      reasonably careful screening examination will elicit physical findings
      beyond the vestibular and acoustic systems indicating a central origin.

2. Perhaps the most common cause of dizziness is simply lightheadedness associated
   with presyncope described above.

3. Finally there are those who are simply complaining of spatial disorientation. We
   maintain our spatial orientation using two sensory systems. We visually fix the
   horizon and through our proprioceptive sensation orient ourselves to gravity. In
   the event that a patient becomes both visually and proprioceptively impaired they
   may experience a sensation of “floating in space,” usually present only when in
   the upright position.
G. “I don’t seem to remember things so well” (Schema #8): This group of patients includes all who develop cognitive disorders. Although most features are indicative of diffuse cerebral disorders, the aphasias, agnosias, and apraxias have focal associations and are seen more often in stroke patients. There is an important distinction between dementias and deliriums. The latter are usually acute and include decreased attention and a fluctuating level of consciousness as well as many features seen in demented patients.

Anatomy Review: Cognitive function is classically felt to be cortically based. However, it is increasingly recognized that subcortical structures such as the basal ganglia, thalamus and cerebellum contribute to cognitive function. Specific areas of the cerebral hemispheres are associated with specific cognitive functions. The dorsolateral frontal cortex is involved in executive function, medial frontal lobes are involved in motivation, and orbital frontal lobes help regulate appropriate social behaviors. The dominant inferior frontal lobes and the posterior superior temporal lobes are the primary cortical areas related to language. The analogous non-dominant areas are important to the affective qualities of speech. The non-dominant parietal areas are concerned with visual spatial function. The occipital lobes process visual information. The mesial temporal lobes are essential to memory function. It is important to recognize that these areas do not function in isolation, but interact with each other and subcortical structures to form circuits and pathways that allow parallel processing of information. A dementia is defined as a process that involves impairment of multiple cognitive domains that is sufficiently severe as to impair social or professional functioning and is not explained by a delirium.

Patient #12: A 72-year-old patient with treated mild hypertension and hypercholesterolemia returns for a routine visit accompanied by his wife. Exam reveals that his blood pressure is 140/70. His wife relates that he often forgets to take his pills and comments that he has overdrawn their bank account. He denies any trouble with mentation, but agrees to a mini-
mental status test. He scores 23 with points lost for delayed recall, serial “7”s, and the interlocking pentagons.

1. Although dementias are usually defined as being chronic, there are acute dementias as well. The best-known are those following traumatic brain injuries. This group includes some of the toxic disorders caused by street drugs and the residuals from viral encephalitis and bacterial meningitis. In these instances diagnosis is seldom a challenge.

2. The chronic dementias are relentlessly progressive. The four major causes of progressive dementia can very often be identified at or shortly after initial presentation.
   a. Alzheimer’s disease is by far the most common and usually presents with memory loss and soon after with compromise of language and executive function.
   b. Vascular dementia is also a common cause of dementia and can coexist with Alzheimer’s disease. The patient will frequently have history of stroke in the past or an MRI scan that is strongly suggestive. Stroke risk factors are usually present. However, they are also frequently present in all of the dementing illnesses. A history of a step-wise progression is often seen.
   c. Frontotemporal dementia is probably next most common. At one time this was referred to as Pick’s disease. There are several variants. The most common form presents with abnormal behavior and apathy. Another form presents with a progressive non-fluent aphasia.
   f. Lewy body dementia usually presents with a combination of Parkinsonian features and memory loss. At least 40% of Parkinson patients will become demented late in their disease. It is unclear in some patients where the line between Lewy body dementia and Parkinson’s disease can be drawn.
   g. There are a host of less common dementing illnesses including tertiary syphilis, AIDS, and chronic alcohol poisoning.

3. Patient #12 has some risk factors suggesting vascular dementia. However, he has never suffered a stroke at least as can be determined by history. Memory loss seems to be the most serious of the present complaints although the difficulty with managing finances suggests that executive functions are beginning to fail. The diagnosis can be confirmed by the mini mental status exam or the MOCA (Montreal Cognitive Assessment), standard screening tests for dementia. MRI may be necessary to make the diagnosis, although vascular dementia and Alzheimer’s disease are often found in the same patient.

4. There are several cognitive phenomena that have focal cerebral associations and maybe seen either in patients with stroke or a progressive dementia. Of these, language disturbances are by far the most common important. The aphasias are disorders of communication and the use of language. The two most common are Broca’s non-fluent aphasia and Wernicke’s fluent aphasia. Numerous other variants have been described. The loss of ability to read (alexia) and loss of the ability to write
(agraphia) belong to this group. It is important on examination to distinguish aphasia from dysarthria (a disorder of enunciation) and aphonia (a disorder of producing sound). Less common are the agnosias (inability to recognize objects) and apraxias (inability to perform a series of skilled movements not attributable to either weakness or sensory loss).

H. “My child isn’t developing normally”: This is a common complaint heard by pediatricians and can encompass a great number of possibilities perhaps best left to the
pediatrician for more details. Some of the major neurologic conditions leading to this complaint are listed below.

1. Babies who never seem able to master any motor skills may well have some form of cerebral palsy. Critical to this diagnosis is the observation that the patient does not progressively worsen and can gain some motor milestones albeit at a slower pace than normal. They will have upper motor neuron findings on exam.

2. Babies who began to develop motor skills and then began to lose milestones may be suffering from progressive spinal muscular atrophy, a disorder sharing many of the features of amyotrophic lateral sclerosis in adults. This can also be caused by one of the many inborn errors of metabolism.

3. Progressive loss of motor skills in older children may be related to Duchenne’s muscular dystrophy or its milder version Becker’s muscular dystrophy. This is also the age group for Friedreich’s ataxia which can be identified by the characteristic ataxia and the common associated skeletal abnormalities.

V. Spinal fluid Interpretation and the Glasgow coma scale

Schema #9: Spinal Fluid Interpretation

| Pressure elevated | • Obstruction of flow  
|                  | • Abnormal material (tumor, hematoma, edema) |
| Granulocytes     | • Bacterial infection (usually meningitis) |
| Lymphocytes over 5 | • Viral or fungal infection  
|                  | • Autoimmune disorder (Multiple sclerosis) |
| Erythrocytes     | • Traumatic tap or post head injury  
|                  | • Subarachnoid hemorrhage |
| Protein over 45  | • Leaking Blood Brain Barrier (inflammation, tumor)  
|                  | • Abnormal protein formation (Multiple Sclerosis) |
| Glucose under 50 | • Bacterial or fungal infection  
|                  | • Carcinoma infiltration of meninges |
Assessing Depth of Coma
Glasgow Coma Scale

- **Eye opening**
  - Spontaneous 4
  - To speech 3
  - To Pain 2
  - None 1

- **Motor response**
  - Obeying 6
  - Localizing to pain 5
  - Withdraw from pain 4
  - Abn flexion 3
  - Abn extension 2
  - None 1

- **Best verbal**
  - Oriented 5
  - Confused 4
  - Inappropriate words 3
  - Incomprehensible 2
  - None 1

15 is normal
“Spells” never score less
Introduction to Clinical Reasoning:

Mood and Anxiety Disorders in Primary Care

Michael J. Roy, MD, MPH

Objectives: At the end of this session, students will be able to:

1. Identify the diagnostic criteria for major depression and anxiety spectrum disorders.
2. Describe appropriate action to take based on PHQ-9 scores for depressive symptoms.
3. Delineate a rationale for selection of an antidepressant medication for a depressed patient.
4. Identify key reasons for referring a patient to a mental health specialist.

Case Vignette

A 35-year-old woman who is a homemaker, wife of a Marine Corps Major, and mother of 3 children, ages 2, 5, and 8, presents with complaints of 2-3 months of fatigue, waking at 3:00 or 4:00 AM most days with difficulty returning to sleep, and headaches. Her husband was deployed to Afghanistan 5 months ago, his fourth deployment in the past 7 years, and she is tired of the frequent moves, being apart from friends and family, and apart from her spouse as well much of the time. She is a college graduate, and hoped to be a teacher, but wonders if she ever will be able to get a break from changing diapers and washing clothes, and really have a career of her own.

Introduction

Mood and anxiety disorders have a wide range of troubling physical as well as psychological manifestations that drive individuals to see their physicians, so that at least one in every four primary care patients has some sort of mental disorder. It is therefore imperative that primary care physicians be comfortable in evaluating and managing patients with depressive disorders. In doing so, it is important to remember these caveats:

- Many patients present with depression by complaining of physical symptoms that do not have readily identifiable causes. In fact, depressed patients report significantly more somatic symptoms than non-depressed patients.
- Most patients are reluctant to seek help from the mental health sector.
- Symptoms of depression in the primary care setting sometimes improve with limited counseling as part of a simple office visit.
- Even when symptoms of depression are blatant, patient resistance to mental health
intervention remains high.

However, there are tools that can facilitate the diagnosis, and therapy is about as effective as that for other common conditions such as diabetes mellitus and hypertension. Moreover, depression is associated with significant morbidity and mortality, both directly, and indirectly through a negative impact on such comorbid medical conditions as cardiovascular disease.

DEPRESSION AND OTHER MOOD DISORDERS

Risk Factors

Though the best approach is to screen all primary care patients for depression, the presence of one or more of the following risk factors should heighten the consideration of screening for depression:

- Female gender
- Postpartum
- History of depression, alcoholism, or other psychiatric illness in first-degree relatives
- Prior episodes of major depression
- Greater risk with first occurrence between ages 20 and 40 years
- Lack of social support
- Significant medical problems such as heart disease, stroke, diabetes mellitus, and cancer
- Frequent use of medical resources in the absence of serious illness
- Several unexplained somatic complaints
- Nicotine dependence or multiple failed attempts at smoking cessation
- Persistent failure to adhere to management recommendations
- Failure to improve as expected

Depressive symptoms are also seen as a side effect of some medications (steroids and the beta-blocker propranolol are the most commonly identified; see Table 3 for others), though it should be noted that virtually any medication may cause an idiosyncratic reaction. Therefore, a history of new medications temporally related to the onset of symptoms should be taken. Careful consideration should be given to stopping a potential offending medication and observing the patient for improvement of the depressive symptoms.

Presentation

Although it is estimated that 88% of individuals with psychological concerns first seek help from a general medical practitioner, five out of six present with physical symptoms that are not even diagnostic criteria for depression, such as dyspepsia, joint or muscle pain, or headaches, rather than complaining of emotional distress such as feeling down or depressed. Recognition of the underlying psychological disorder only occurs about half the time in such patients, whereas the etiology is almost invariably identified in patients with clear psychological complaints. Physical symptoms have many potential etiologies, and primary care physicians may be more attuned to seeking organic (e.g., heart disease, malignancy) rather than psychological causes. However, considering mood and anxiety disorders up front is far better than just doing so later after everything else is excluded. Considering psychological conditions only as a diagnosis of exclusion for symptoms with no clear organic basis can lead to numerous costly and potentially
harmful diagnostic tests, delaying effective treatment, and undermining satisfaction in patients who desire dialogue on psychosocial issues. Stigma surrounding mental illness can lead both patients and physicians to avoid direct discussion of mood and anxiety disorders. Patients either mention their symptoms at the end of an appointment (usually while you’re trying to usher them out the door!) or fail to acknowledge them at all; physicians may avoid discussion for fear of embarrassing patients. Ironically, studies indicate that patients actually derive greater satisfaction from discussing psychosocial issues than biomedical subjects. Onerous time constraints are an additional obstruction to patient-physician discussion of mood and anxiety complaints.

**Diagnosis**

**Major Depression**

Depression is the second most commonly encountered condition in primary care, following hypertension. About one in six Americans will suffer an episode of major depression in their lifetime, and for most it will be a chronic disease, with a recurrence rate of 50% after their first episode, 70% after the second, and 90% after the third. Depression may occur at any age, but the average age of onset is in the third decade of life.

To diagnose depression, the physician must ask about these nine symptoms:

- Depressed mood
- *Sleep* disturbance
- Loss of *Interest* or pleasure, i.e., anhedonia
- Feelings of *Guilt* or worthlessness
- Low *Energy*
- Poor *Concentration* or memory
- Appetite disturbance
- Psychomotor agitation or retardation
- *Suicidal* ideation

At least five of these symptoms must be present for most of the previous 2 weeks for a diagnosis of major depression. A popular mnemonic, **SIG = E CAPS** (“the prescription for depressed patients is energy capsules”) facilitates recall of the eight criteria that may accompany depressed mood.

Diagnosis can be further facilitated by the use of the Nine-Item Patient Health Questionnaire (PHQ-9). The PHQ-9 is ideal for screening for depression, uniquely combining the following features:

- brief and compatible with time constraints;
- easy and inexpensive to administer;
- makes accurate, validated diagnoses;
- educates patient and provider;
- provides a score to connote severity and to facilitate longitudinal monitoring;
- use has been associated with improved outcomes (in conjunction with provider education and mental health consultation).

Since the nine items are taken directly from the diagnostic criteria for major depression (see PHQ figure), the instrument facilitates rapid diagnosis, with a cutoff score of 10 having 88% sensitivity and specificity for major depression. PHQ-9 scores correlate strongly with self-
reported quality of life, interference of symptoms with usual activities, number of physician visits, and difficulties at work, at home and with others. Most valuable of all, the PHQ-9 score can be used as blood pressure or blood sugar are used to follow hypertension and diabetes mellitus, respectively, enabling a primary care provider to follow a patient’s score to guide management as follows:

<table>
<thead>
<tr>
<th>PHQ-9 Score</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>none</td>
</tr>
<tr>
<td>5–9</td>
<td>watchful waiting, with periodic screening</td>
</tr>
<tr>
<td>10–14</td>
<td>treatment plan, considering counseling, follow-up, and pharmacotherapy</td>
</tr>
<tr>
<td>15–19</td>
<td>immediate implementation of therapy</td>
</tr>
<tr>
<td>≥ 20</td>
<td>pharmacotherapy and, if severe impairment or poor response to therapy, expedited referral to a mental health specialist</td>
</tr>
</tbody>
</table>

Though the full instrument takes less than a minute for most patients to complete, an even easier approach to initial screening is to start with only two of the items: 1) little interest or pleasure in doing things, and 2) feeling down, depressed, or hopeless. Since one of the two has to be positive to make a diagnosis of depression, this has high sensitivity, and specific diagnosis can then be made with administration of the full instrument. In fact, even a single question, “Have you felt sad or depressed much of the time in the past year?” is nearly as sensitive (85%) and specific (66%) as more comprehensive questionnaires. The characteristics of this “diagnostic test” compare favorably with many tests commonly used by primary care providers to screen for cancer or heart disease.

Numerous randomized controlled trials have shown that major depression can be improved by medication, psychotherapy, and electroconvulsive therapy. Thus, any patient meeting diagnostic criteria should have some sort of treatment plan established, even if they have an underlying medical condition (e.g., anemia with related fatigue) which contributes to the diagnosis. Those who do not have depression will typically have only one or two such symptoms so there is little likelihood of falsely making a diagnosis. In fact, comorbid depression dramatically increases the morbidity and mortality of common medical conditions such as diabetes mellitus and coronary artery disease.

When depression is identified, how thoroughly should a physician assess for potential underlying causes? A complete history and physical examination, with attention to new medications and to previously noted risk factors, is usually sufficient, with additional studies ordered only if they are suggested on this initial evaluation. For example, thyroid tests only need to be ordered if non-depression-related thyroid signs (e.g., tachycardia, bradycardia, ocular findings, or skin changes are identified); thyroid disease is no more common in depressed patients than in the general population.

**OTHER MOOD DISORDERS**

Diagnostic criteria for other mood disorders can be found in Appendix 1.

**Bipolar Disorders**

Bipolar disorders (BPD) deserve particular attention because the initiation of the most popular treatment for depression can trigger a manic or psychotic episode in a patient who actually has bipolar disorder. Bipolar disorder is also commonly known as manic-depressive disorder, and features two major types. Type I features manic or mixed manic-depressive episodes, usually with periods of major depression as well, whereas Type II is characterized by
periods of major depression and a history of at least one hypomanic period. A manic episode is a period of at least a week that is marked by an abnormally and persistently elevated, expansive, or irritable mood. Three or more of these symptoms should be also be present during this time: inflated self-esteem or grandiosity; decreased need for sleep; unusually pressured, rapid, and/or prolonged speech; racing thoughts or flight of ideas; distractibility; increased goal-directed behavior (e.g., sexual, political, religious); and excessive involvement in activities that have the potential for significant adverse consequences (e.g., spending sprees and sexual indiscretions), often characteristic of impaired judgment. Hypomanic episodes may be as short as 4 days, characterized by a clear change in functioning that is less than marked impairment, in addition to having three or more of the accompanying manic symptoms. Psychotic features are more common in bipolar disorders than with major depression. Bipolar disorder is less common than major depression, with a prevalence of only 1-4% in the US. However, one study found that nearly 20% of individuals who did not respond to antidepressant treatment for unipolar depression met criteria for previously undiagnosed BPD. The Hirschfeld Mood Disorders Questionnaire (See Table 3) is a brief, validated screen for BPD. Though primary care physicians do not often diagnose BPD, it is important to briefly assess for a personal or family history of diagnosed BPD, or to ask some of the characteristic features in Question 1 of the MDQ before starting antidepressant therapy. A good screening question is: Have you had a period of several days or more where you have had a lot of energy, required little or no sleep, or had difficulty keeping up with thoughts racing through your head? The full MDQ should be administered to those who don’t respond to an initial course of therapy for unipolar depression. Since pharmacotherapy for BPD is more complicated and toxic than for unipolar depression, a psychiatrist should be involved in the care of most BPD patients. While lithium has long been used to treat BPD, it has a narrow therapeutic window, is teratogenic, nephrotoxic, and can cause hypothyroidism. Alternative treatments include the anticonvulsants valproic acid, carbamazepine, and lamotrigine, as well as second generation antipsychotics such as quetiapine, olanzapine, and risoperidol. Adjunctive psychotherapy including psychoeducation is also beneficial. Pharmacotherapy should be continued for at least a year after achieving a response; most will require lifelong treatment.

Persistent depressive disorder
Previously characterized as dysthymia, this is a milder but more chronic depressed mood present for at least 2 years in adults or at least one year in children or adolescents, with symptoms present for most of the day, more days than not, and depression-free intervals lasting no more than 2 months. This is more resistant to therapy than other forms of depression, usually progresses to major depression over time. In addition to depressed mood, diagnosis requires the presence of two or more of the following: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. A useful initial screening question is: Have you felt down or depressed for more days than not for at least 2 years?

Minor or Subthreshold Depression
Patients with symptoms of depression that are fewer in number or shorter in duration than required to diagnose the above conditions may have “subthreshold”, “subsyndromal”, or “minor” depression. Although this category not been given as much attention as major depression, since
minor depression four times more common, on a population basis it is actually responsible for
greater disability, use of medical services, and social morbidity. Minor depression is
characterized by at least two weeks of two to four depressive symptoms, with associated
impairment in social functioning, mental health, and health perceptions.

Bereavement
While the reaction to the death of a loved one may include some features of major depression,
(e.g., depressed mood, sleep disturbance, and altered appetite), patients who still meet criteria for
major depression two months after the death should be treated. Treatment should also be
considered even earlier if the response includes: guilt about things other than what the individual
did or did not do at the time their loved one died; excessive preoccupation with worthlessness;
thoughts of death beyond wishing that they had died with, or instead of, the deceased; striking
psychomotor retardation; prolonged, marked functional impairment; hallucinations other than
transiently hearing the voice of, or seeing images of, the deceased.

Seasonal Affective Disorder
Seasonal affective disorder (SAD) is a cyclical disorder featuring onset of depressive symptoms
at a particular time of year (usually fall or winter) with full remission at other times of the year.
A useful initial screening question is: Do your symptoms seem to recur at the same time each
year? A good reason to differentiate SAD is because bright light therapy is particularly effective,
though both SSRIs and cognitive behavioral therapy also seem to have an adjuvant effect.

Affective Disorders Specific to Women

Premenstrual dysphoric disorder (PMDD)
This diagnosis should be considered in women with mood symptoms that are temporally
related to their menstrual cycle. Symptom onset should be in the week prior to menses with
complete remission within a week after menses. Five or more of the following symptoms should
be reported, including at least one of the first four:
• markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts;
• marked anxiety, tension, feelings of being keyed up or on edge;
• marked affective lability;
• persistent and marked anger or irritability or increased interpersonal conflicts;
• decreased interest in usual activities;
• subjective sense of difficulty concentrating;
• lethargy, easy fatigability, or marked lack of energy;
• marked change in appetite, overeating, or specific food craving;
• hypersomnia or insomnia;
• subjective feeling of being overwhelmed or out of control;
• other physical symptoms such as breast tenderness or swelling, headaches, joint or muscle
  pain, a sense of bloating, weight gain.

The symptoms should impair functional status at work, school, or in social settings;
should persist for at least two consecutive cycles; and should not merely represent an
exacerbation of another mental disorder. A useful initial screening question is: Do your
symptoms seem to be related to your menstrual cycle? Full-blown PMDD has been identified in 3% to 5% of menstruating women, and subthreshold symptoms are even more common. Effective responses have been demonstrated with both cyclical and continuous treatment with selective serotonin reuptake inhibitors (SSRIs).

Postpartum depression
Postpartum blues, characterized by 1 to 4 days of labile mood and tearfulness, has been reported by at least 50% to 80% of women within 5 days after delivery. Postpartum depression has been identified in 10% to 15% of women at 3 to 6 months postpartum, more frequently in those with a psychiatric history. Life stressors related to delivery and childcare are additional risk factors. Psychosis, typically beginning within 3 days after delivery, is far less common than depression and may occur with or without depressive symptoms. Psychosis has a good prognosis but often recurs with subsequent pregnancy. Risk factors include prior depression or other psychiatric diagnoses, life stressors, stillbirth, and miscarriage.

Perimenopausal Symptoms
Although initial studies indicated an increased prevalence of depression in women at the time of menopause, these studies had methodologic problems. While mild mood and anxiety symptoms are common perimenopausally, there does not seem to be an increased rate of full-blown disorders. However, women with menopausal symptoms do have improvements in depressive symptoms and emotional measures of quality of life with hormone replacement therapy.

Mixed Anxiety and Depression
Some patients with several features of depression that are accompanied by excessive worrying or other symptoms of anxiety disorders do not meet the criteria for major depression, generalized anxiety disorder, or panic disorder. Evidence of associated functional impairment and increased healthcare utilization suggests that “Mixed Anxiety and Depression” is a significant diagnostic worth attention. However, it may be more useful to consider that depressive and anxiety disorders represent part of the same spectrum, with many individuals having some features of each. Since most second generation antidepressants appear to be effective across the full spectrum of anxiety disorders, specific identification of a disorder may often be of little use.

Comorbidity
Two thirds primary care patients with a depressive disorder have at least one other mental disorder. About 30% of patients with an anxiety disorder also have depression. A number of other psychiatric illnesses have an increased prevalence of depression:

- substance abuse, 15% to 25%
- eating disorder, 25% to 50%
- schizophrenia, 28%
- dementia, 30% to 40%
- obsessive-compulsive disorder (OCD), 75%

Suicidal ideation
Suicidal ideation is a core symptom of depression. Depressed primary care patients have a lower rate of suicide than depressed patients seen in psychiatric practice, in part primary care physicians who identify suicidal ideation in patients usually refer them to psychiatrists. On the other hand, at least half of suicide victims are reported to have visited their physician within 1 month, and more than 70% within 2 months, before their death, so primary care physicians must know how to detect and evaluate suicidal ideation.

**TREATMENT OF DEPRESSION**

Antidepressant options for depression have increased dramatically in number in recent years, and many of the newer agents are far better tolerated than the original tricyclic antidepressants. There are also a variety of nonpharmacologic therapies for depression that physicians should also understand. The number and duration of symptoms, as well as the degree of associated dysfunction, should all be taken into account in determining an initial plan. The PHQ-9 can be especially helpful in this regard. There are occasional patients with major depression, with recent onset of symptoms and mild to modest impairment, for whom initial counseling and prompt follow-up may be appropriate, particularly those who require a little time to accept the diagnosis and prepare for therapy. There are also patients with fewer than five criteria for major depression whose symptoms are persistent and distressing, such as those with mixed anxiety and depression, for whom immediate initiation of antidepressants is best. A strong family history of depression, as well as a personal history of prior depression or suicide attempt, favor early treatment. Serious suicidal ideation, psychotic depression, delusions (of guilt, persecution, or nihilism), hallucinations, and evidence of bipolar disorder are all good reasons to promptly refer to a psychiatrist.

Educating the patient about depression, or recommending sources of information for them to learn more about their condition, is an important part of the initial approach to the patient with a mood or anxiety disorder. This can help the patient appreciate that it is not his or her fault that they are depressed. Education of family members and friends may be equally important. Education may also help to improve adherence, since many patients discontinue therapy as soon as they feel better, putting themselves at significant risk for relapse. Cognitive-behavioral and interpersonal psychotherapy are as effective as medication in the treatment of mild to moderate depression, and psycho-education is an important element of such approaches.

Evaluating and promoting support systems for patients is another important piece of management. Having friends and family who can help the depressed patient through to recovery is critical. It is not uncommon for depressed patients to withdraw, and to also spend very little time in recreational or other enjoyable pursuits...sometimes they may need a “prescription” for this! Therefore, it is useful to ask about work and social life during a patient’s clinic visits to see if there are areas to focus on as the patient’s depression improves. Encouraging patients to avoid high-stress situations, get help with housework or meals, take a weekend off, or attend couples or family therapy can have high yield.

There are a variety of resources available to assist in educating patients. The National Institute of Mental Health has a mood and anxiety disorders program (MAP, 866-627-6464) with free information, available in many languages, for patients, families, and employers. They also provide information about treatment trials, which may be useful for patients who have unusual complications or are not responding well to treatment. Useful websites include those of the Depression and Bipolar Support Alliance (DBSA, formerly the National Depressive and
Manic Depressive Association, or NDMDA, [www.ndmda.org](http://www.ndmda.org) and the Depression and Related Disorders Association (DRADA, [www.drada.org](http://www.drada.org)). Patients who have experienced mood disorders run both organizations. They provide informational resources through mail-order bookstores and sponsor support groups for patients and family members coping with mood disorders. These organizations assist patients and families in coping with the symptoms of depression before recovery occurs. Useful websites for physicians include the MacArthur Foundation Depression and Primary Care website ([www.depression-primarycare.org](http://www.depression-primarycare.org)) and the American Psychiatric Association ([www.psych.org](http://www.psych.org)).

**Pharmacotherapy**

There are a range of options available for patients with unipolar major depression (it should be noted that those with bipolar affective disorder require mood stabilization with lithium, carbamazepine, sodium valproate, or some of the newer atypical antipsychotic agents; use of standard antidepressants, especially SSRIs, may trigger more rapid and treatment-resistant cycling between different mood states).

Unipolar major depression can be treated with medication, certain specific forms of psychotherapy, and neuromodulation. Beyond brief counseling, medication is usually the only realistic intervention that is readily available in primary care. There is not usually sufficient time or expertise for psychotherapy. All antidepressants are of comparable efficacy, so the selection of a particular agent is usually based on predominantly on its side-effect profile. The first medication usually works 50% to 70% of the time. SSRIs should be the first choice for most patients, since they are relatively well tolerated, safe, and effective. SSRIs are also effective for many other psychiatric conditions (e.g., OCD, anxiety, and PMDD) that are often comorbid with depression. Tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) should rarely be the first choice for depression, especially in primary care, because of their high toxicity and interactions with other medications and foods. However, if a patient had excellent results with a TCA previously, it should be considered to treat a recurrence of symptoms. The ARTIST (A Randomized Trial Investigating SSRI Treatment) trial found similar efficacy for three of the SSRIs that are most widely prescribed in the United States—fluoxetine hydrochloride, paroxetine hydrochloride, and sertraline hydrochloride—and it is likely that the other available SSRIs are also equally effective. Selection might be based on the cost for some patients, but most often the determination will be based on side effect profile. For example, paroxetine is more likely to cause weight gain than other SSRIs, so it should be avoided in patients who are concerned about their weight. Paroxetine hydrochloride has a shorter half-life than the others and consequently may be more likely to cause serotonin-withdrawal symptoms (headache, tremulousness, nausea) in noncompliant patients, though withdrawal symptoms may occur with the use of other SSRIs as well. Fluoxetine hydrochloride and paroxetine hydrochloride have a greater effect on the liver’s P450 system, making interactions with some other drugs a potential concern.

Although the SSRIs are far better tolerated than TCAs, they are not universally well tolerated (anorgasmia and other effects on sexual function are common), and they don’t work for everyone. There have also been some concerns about SSRIs being associated with a higher rate of suicide attempts—this is controversial and may occur with any antidepressant, not to mention in untreated depression, but some theorized that there might be a real association since SSRIs
might be more likely provide the energy to act on prior suicidal impulses, and there may be a window in which one is at significantly greater risk. Primary care physicians should try to monitor patients closely after initiating therapy, including assessment for suicidal ideation, and nurses or case managers may be helpful in this regard. Fortunately, more recent better quality studies have indicated that SSRIs are not more likely to increase suicide risk in adults, and may even lower the risk in older adults, but there is still some concern in adolescents. The STAR*D trial (described in more detail below) has shown that patients who do not respond to one SSRI have about a 25% response rate to another antidepressant, and use of a different SSRI is equally effective as switching to another class of antidepressant. Physicians should still be comfortable prescribing at least a few other classes of antidepressants in addition to SSRIs for those who do not respond initially.

The 5HT-2 antagonist trazodone hydrochloride rarely causes sexual side effects, and is especially good in promoting sleep, but causes priapism in about 1 in 6,000 men.

Venlafaxine hydrochloride acts like an SSRI at lower dose ranges. However, when the dose is increased, it also has significant norepinephrine reuptake inhibition, becoming an “SNRI”. It is generally effective and well tolerated, without significant interaction with other medicines, but it can exacerbate hypertension, a highly prevalent problem in primary care.

Two useful antidepressants that do not fit neatly into another category are bupropion hydrochloride and mirtazapine. Bupropion, which is also approved for smoking cessation, can be a great choice for a depressed patient who also wants to quit smoking. It rarely causes sexual side effects, but insomnia can occur in some patients. It can also lower the seizure threshold, so it should not be used in patients with a history of seizures. Mirtazapine is sedating and causes weight gain, making it a consideration for patients with insomnia or who have had undesirable weight loss with their depression. Each might also be used as adjunctive therapy in conjunction with lower doses of SSRIs for those who do not tolerate higher doses but have a partial response to a lower dose.

TCAs are as effective as any other class of antidepressants if patients actually continue to take them and should be considered for patients who did not respond to the first choice of medication, or can also be considered as adjunctive therapy in those with a partial response to the first agent. Nortriptyline hydrochloride has less anticholinergic side effects than others in its class and has the advantage of being able to monitor blood levels, which can help in assessing compliance and confirming a therapeutic level.

Finally, some patients may ask about or even self-medicate with alternative medicines, particularly St John’s wort (Hypericum perforatum). Although some studies have shown efficacy for St John’s wort in mild to moderate depression, larger and more rigorous trials have generally been negative. Since its production is not under the control of the US Food and Drug Administration, there are also concerns about the quality and uniformity of various formulations.

At least one third of patients stop antidepressant medication within the first several weeks and half or more stop before completing the recommended 6 to 9 months of therapy. Patients should be informed that side effects, if they occur, typically diminish within the first several weeks and that while the benefits are usually not immediate, they tend to develop gradually over the first 2 to 6 weeks of therapy. It is important to remind patients of the need to continue to take medicine even if feeling better, to prevent relapse. Patients who have a first episode of depression should continue treatment another 4 to 9 months after symptom resolution; this decreases the chance of relapse from 65% to 20%. Since half will remain symptom-free the rest
of their lives, a trial of treatment cessation is reasonable, but for those who had a particularly severe episode, or who have a strong family history of depression, longer treatment courses may be warranted. In addition, patients with two prior episodes have a 70% chance of recurrence. Although at least 6 to 9 months should elapse before medication is discontinued in these patients, greater consideration should be given to prolonged and/or lifetime therapy based on clinical circumstances. Many factors contribute to this decision, such as episode severity, time interval between episodes, and family history. Patients with three or more episodes or those with poor interepisode recovery should be considered for lifetime antidepressant therapy because they have a 90% risk of recurrence.

If a 50% reduction in symptoms is not achieved by 4 to 6 weeks, the dose should be increased, and if a near complete response is not achieved with maximal doses by 10 to 12 weeks, adjunctive therapy or a change in therapy should be considered. Monitoring response to therapy with the PHQ-9 score can be very helpful in judging whether a partial or full response is achieved. Just as for hypertension and diabetes mellitus, successful treatment of depression often requires more than one medication. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial treated more than 4,000 depressed patients at multiple sites, providing the best evidence to date of the true effect of pharmacologic therapy for depression: treatment with the SSRI citalopram alone achieved a 30% remission rate. While this rate appears relatively low, the great majority of these patients had recurrent depression, and the mean duration of depression was 16 to 17 years. The STAR*D investigators assigned non-responders to bupropion, sertraline, or venlafaxine, and found essentially equivalent responses to each, roughly 25%. A parallel study augmented the citalopram with bupropion and found a 30% response rate. The best approach seems to be to add an adjunctive treatment for those who achieve a partial response to maximal initial monotherapy, but an alternative monotherapy is a best for those with little or no response to the initial agent. The initial and second choice should be chosen primarily by matching the individual side effect profile to the individual patient.

**Psychotherapy**

Multiple forms of psychotherapy have been found effective in randomized controlled trials, including interpersonal psychotherapy (IPT), cognitive-behavioral psychotherapy (CBT), problem-solving therapy (PST), and behavior therapy (BT). Psychotherapy works as well as pharmacotherapy for mild to moderate depression, but it can take longer to produce improvement—up to 6 to 8 weeks, or perhaps 2 to 3 weeks longer than with medication. For more severe depression, there is good evidence that a combination of psychotherapy and pharmacotherapy is superior to either alone. Psychotherapy mandates that the patient is an active participant, which poses an initial hurdle, but it can ultimately be quite valuable for the patient to take this more active role. Relapse is less likely after successful psychotherapy than after pharmacotherapy.

Combined medication and psychotherapy, compared to medication alone, is cost effective, saving money by lowering hospitalization rates and reducing lost workdays. It also achieves better outcomes, especially in more severe depression. Psychotherapy is advisable as an adjunctive therapy for seriously depressed patients, as well as for those with comorbid panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and eating disorders.
Neuromodulation

Neuromodulation includes electroconvulsive therapy (ECT), as well as more recently developed alternatives such as the more benign transcranial magnetic stimulation (TMS) and the more invasive but more directed deep brain stimulation (DBS). ECT is clearly effective in treating depression, but it is usually reserved for severe or treatment-resistant depression, especially in severe cases such as those with profound suicidal ideation or psychotic features, where a rapid response to therapy is particularly desirable. Although reviews and metaanalyses indicate that ECT likely has a higher rate of response, and more rapid response, than either sham ECT or pharmacotherapy, there are methodologic limitations to some of the studies, and there is also in no small part due to Hollywood, there is greater stigma associated with ECT, so it is often reserved as a last resort for those who have failed multiple medications. This is not an unreasonable approach, since ECT has not always proven as effective in the community as in controlled trials. DBS has had a remarkable impact in some cases of treatment-resistant depression but requires further study to both perfect the technique and delineate optimal use. TMS is non-invasive, relying upon the external application of magnetic coils, and seems to have some promise, with studies currently in progress to define the scope and strength of its effect.

Disorders With Specific Therapies or Considerations

Individuals with seasonal affective disorder respond well to light therapy (use of artificial light to replace seasonally diminished sunlight) with or without adjunctive medications. Light therapy also seems to have some benefit in mild to moderate non-seasonal depression.

Patients with premenstrual dysphoric disorder respond to either cyclic or continuous therapy with SSRIs. In general, SSRIs are particularly effective for a wide spectrum of mood and anxiety disorders. In particular, one or more types of antidepressants have proved efficacious for panic disorder, generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder. However, cognitive behavioral therapy is the first choice for most of these anxiety spectrum disorders. The fact that many depressed patients have other comorbid mental disorders, coupled with their benign side-effect profile, makes antidepressants particularly appealing as first-line therapy for many patients with this type of mood disorder.

Referral

A common question that primary care physicians have about their involvement with depressed patients is when to make a referral. This is, of course, a function of the knowledge and skills of the physician considering the referral. Some physicians have had excellent training in the care of uncomplicated depression, while others feel uncomfortable addressing emotional distress in patients. Referral therefore depends on each physician’s comfort level with particular patient presentations. However, some patients invariably need the services of a psychiatrist (Table 5). They include those with treatment resistance, suicidal or psychotic behavior, the need for combination or extraordinary medication, bipolar symptoms or history, or the need for hospitalization. Some primary care physicians prefer early referral of patients, even when they could handle the case themselves. This may be because their practice demands full attention to medical conditions with little time devoted to the emotional difficulties of their patients. The referring physician should prepare a patient for referral and provide basic information about depression. There are also patients whom the primary care physician is comfortable treating.
pharmacologically but refer for adjunctive psychotherapy: this includes patients who seem to have significant insight that seemingly could benefit from greater attention and/or expertise than the primary physician is able to provide. Regardless of the indication for referral, the primary care physician should schedule the patient for follow-up, demonstrating continued involvement and interest in their care and preventing feelings of abandonment.

**ANXIETY DISORDERS**

The anxiety disorder spectrum includes generalized anxiety disorder (GAD), panic disorder with and without agoraphobia, social anxiety disorder, and specific phobias; though now distinguished from the anxiety spectrum, posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) each enough overlap with these disorders that the same diagnostic instruments have moderate efficacy in identifying them as well. Overall, anxiety disorders are perhaps even more common than depression, and total direct and indirect costs are similar to those associated with depression.

**Generalized Anxiety Disorder and Panic Disorder**

GAD has a prevalence of 4-6%. The disorder features: excessive anxiety and worry about a variety of events or activities over at least a 6-month period; difficulty exercising controlling over worrying; several symptoms associated with the anxiety, such as fatigue, irritability, restlessness, sleep disturbance, and difficulty concentrating; functional impairment; and the symptoms are not explained by the presence of another Axis I disorder, another medical condition, or medication. GAD can be easily screened for, either by asking, “Are you bothered by nerves?”, which had a 100% sensitivity and 59% specificity in a study of primary care patients, or with the two-item GAD-2. The GAD-2 had a sensitivity of 86% and specificity of 83% when using a cut-off score of 3, faring about as well as a 7-item scale. Increasing its utility to the primary care physician, the GAD-2 is also effective at identifying other anxiety disorders: using a cut-off of 2, its sensitivity was 91% for panic, 85% for social anxiety, 86% for PTSD, and 86% for any anxiety disorder. The GAD-2 was recently combined with the two highly sensitive screening questions for depression regarding anhedonia and feeling down, depressed, or hopeless. The composite instrument, the PHQ-4, was validated in more than 2,000 primary care patients, and demonstrated a strong correlation with functional status, disability days, and health care utilization.
Panic disorder can be one of the most frustrating of all medical conditions, with the average patient having been seen by many physicians, and having had extensive testing including repeated “rule outs” for myocardial infarctions, Holter monitors, and invasive assessments such as cardiac catheterization and esophagogastroduodenoscopy. In fact, panic disorder is associated with the highest utilization rates of medical services of all mental health problems. However, upon identification of the correct diagnosis and initiation of effective treatment, these can be among the most satisfying of all patients. Panic disorder is characterized by recurrent, unexpected panic attacks which feature the abrupt onset of numerous somatic symptoms such as palpitations, sweating, tremulousness, dyspnea, chest pain, nausea, dizziness, and numbness. Symptoms typically peak within 10 minutes of onset and attacks usually have a duration from 15 to 60 minutes. While as many as 30% of Americans may experience a panic attack during their lifetime, the prevalence of panic disorder is only 1-2%, since its diagnosis also requires that one or more of the attacks be followed by at least a month of persistent worry about having another attack, about the implications of the attack or its consequences, or a significant change in behavior related to the attacks. Up to half of those with panic disorder also have agoraphobia, characterized by a fear of being in places from which escape might be difficult (e.g., in crowds, on a train or plane, on a bridge or in a tunnel. Individuals with agoraphobia either avoid such situations, or endure them with marked distress, even experiencing symptoms of panic.

Comorbid medical and/or psychiatric conditions are present in most patients with GAD; panic disorder frequently coexists with major depression, GAD, PTSD, and/or other psychiatric disorders. While GAD and panic should be considered up front rather than just as a diagnosis of exclusion, particular conditions that could be etiologic, and therefore should be evaluated for in the history and physical exam, include hyperthyroidism, pheochromocytoma, Cushing’s syndrome, insulinoma, anemia, asthma or vocal cord dyskinesia, and cardiac conditions such as angina, mitral valve prolapse and atrial fibrillation or another arrhythmia. Accordingly, symptoms that should be asked about, and carefully reviewed when present, include weight loss, heat intolerance, diaphoresis, headaches, lightheadedness, chest pain, palpitations, and dyspnea. Caffeine intake, as well as ingestion of drugs of abuse such as cocaine or amphetamines, should be assessed. Key physical exam elements include the vital signs, eye exam including an

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**GAD-2 Screen for Generalized Anxiety Disorder**

During the past month, have you been bothered a lot by:

1. Nerves or feeling anxious or on edge?
   - a. Not at all (0)
   - b. Several days (1)
   - c. More than half the days (2)
   - d. Nearly every day (3)

2. Worrying about a lot of different things?
   - a. Not at all (0)
   - b. Several days (1)
   - c. More than half the days (2)
   - d. Nearly every day (3)
assessment of extrinsic ocular muscles and for exophthalmos, thyroid exam with a check for a
bruit, cardiac and pulmonary exam, and assessment of the hair and skin. Laboratory testing need
not be extensive—it should be guided by the findings on history and physical—but a complete
blood count, serum chemistry panel, thyroid function tests, urinalysis, and electrocardiogram are
prudent. Additional studies should not be routine, but may be necessary to rule out differential
diagnoses depending upon the presenting signs and symptoms.

Effective therapies are available for both GAD and panic disorder. Cognitive Behavioral
Therapy (CBT) is the best-evidenced non-pharmacologic therapy for these conditions, supported
by many randomized controlled trials and several metanalyses. Several recent studies provide
evidence that relatively brief courses of CBT, or even self-help CBT, may be effective for panic,
whereas GAD may require longer courses, such as 12 to 20 sessions. CBT seems to have a more
durable effect, with lower relapse rates than pharmacologic therapy, and use of CBT in patients
who failed pharmacologic therapy also showed significant efficacy. However, there is good
evidence that SSRIs as well as venlafaxine are far superior to placebo in the treatment of both
GAD and panic disorder. Panic disorder stands alone among the anxiety spectrum disorders as
the condition for which there is clear evidence that the combination of CBT and
pharmacotherapy is superior to either alone. Second-line therapies have been shown to have
some utility but all have drawbacks, including tricyclic antidepressants such as imipramine (risk
of fatal cardiac arrhythmias in overdose, as well as anticholinergic side effects), benzodiazepines
(dependence and tolerance issues), and azapirones such as buspirone (less compelling evidence,
and relatively delayed onset of action).

Social Anxiety Disorder
Formerly known as social phobia, social anxiety disorder is one of the most common
psychiatric disorders, with a point prevalence of 7% and a lifetime prevalence of more than 13%.
The primary feature is a severe and persistent fear of social or performance situations, such as
public speaking or taking an exam. In such situations, blushing and other anxiety symptoms are
commonly experienced, though full-blown panic attacks are usually not. Individuals with social
anxiety disorder recognize that their fear is excessive (except children sometimes do not), are
characteristically markedly distressed about the condition, and either avoid precipitating
situations or endure them with dread. Onset is usually early in life, frequently heralding
subsequent psychiatric diagnoses. CBT, especially regimens that incorporate elements of either
imaginal or virtual exposure therapy, has been proven effective for social anxiety disorder, and
SSRIs are the best-evidenced pharmacotherapy.

Posttraumatic Stress Disorder
Posttraumatic stress disorder (PTSD) is unique among the anxiety disorders because it
has a clear precipitant—exposure to a traumatic event, such as war, disaster, or an assault that
involves an actual or threatened death or serious injury to one’s self or others. To meet criteria
for PTSD, the trauma must be followed by at least one month of disabling symptoms in four
different categories (see table): intrusive elements such as flashbacks and nightmares, negative
changes in cognition, avoidance of reminders of the trauma, and heightened arousal or
hyperreactivity to external stimuli. PTSD was codified in the aftermath of the Vietnam War, but
the symptoms and associated functional impairment it represents have been known for centuries.
Homer depicts symptoms of this disorder in his account of Achilles in The Iliad, and hundreds of
reports have appeared in the medical literature from the American Civil War, both World Wars, and numerous other national and international conflicts. Most recently, PTSD has been well documented after the terrorist attacks of 9/11/2001, Hurricane Katrina, and war in Iraq.

Although a majority of the general population has experienced trauma sufficient to induce PTSD, most of the exposed are resilient, so that the overall likelihood of developing PTSD after a traumatic event is estimated at 9% to 25%. Community surveys identify a 2-5% point prevalence and 8-12% lifetime prevalence for PTSD. PTSD was documented in 39% of patients referred by their primary care providers for mental health services based on suspicion of depression or anxiety, but like most mental disorders, PTSD often goes undiagnosed in primary care, and such patients often do not see mental health specialists. The gold standard instrument for the diagnosis of PTSD is the Clinician-Administered PTSD Scale (CAPS), but it is 17 pages long and takes about an hour for a professional to administer, rendering it impractical for use in primary care. The PTSD Checklist (PCL) is a 21-item screen which can be self-administered, and has had moderately good sensitivity and specificity, but a newer, 4-item screen, the PC-PTSD, has fared at least as well in some studies, using a cut-off of 2 or more positive replies (see table).

### PC-PTSD

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever had any experience that was so frightening, horrible, or upsetting, that in the past month you:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Have had nightmares about it or thought about it when you did not want to?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>2. Tried hard not to think about it or went out of your way to avoid situations that remind you of it?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>3. Were constantly on guard, watchful, or easily startled?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4. Felt numb or detached from others, activities, or your surroundings?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Successful treatment of PTSD should ideally improve quality of life in multiple domains, improve functional status, decrease symptom severity, and reduce vulnerability to subsequent stress. The most proven pharmacologic therapies for improving all categories of PTSD symptoms are selective serotonin reuptake inhibitors, but the best reported response rates are only 40-60%, and relapse after discontinuation of medication is common. The alpha-blocker prazosin appears to reduce the frequency and intensity of intrusive nightmares. A meta analysis comparing trials of pharmacotherapy to psychotherapy found that while both were effective, the effect size was significantly greater (1.17 vs. 0.69), and the drop-out rate was lower (14% vs. 32%), for psychotherapy. The preferred treatment is cognitive behavioral therapy (CBT) with exposure therapy, which more frequently achieves a response and has more durable benefit. CBT characteristically includes elements of psycho-education, controlled breathing and relaxation techniques, and cognitive restructuring. Exposure therapy helps individuals to confront stimuli (e.g., thoughts, images, objects, situations, or activities) associated with their traumatic experience through progressively more intense exposure, providing the therapist with opportunities to identify and neutralize behavioral cues; imaginal exposure has been the most
widely employed approach, whereby the therapist asks the patient to recall their traumatic experience in progressively greater detail. This is often supplemented by in vivo exposure in which the patient confronts real life circumstances that have been difficult because of precipitating memories or emotions related to prior trauma. Unfortunately, since avoidance is a cardinal feature of PTSD, a significant number are unwilling or unable to effectively engage in imaginal exposure. Recent studies have shown some success in overcoming avoidance through the application of virtual reality, effectively immersing patients in an environment reminiscent of their trauma to facilitate recall. Overall, a recent meta-analysis found that while CBT was effective for all anxiety spectrum disorders, the effect was most robust for GAD and PTSD.

**Obsessive Compulsive Disorder**

The hallmark of obsessive compulsive disorder (OCD) is the presence of recurrent obsessions and/or compulsions that are of sufficient severity to occupy at least an hour per day, or to result in marked distress or functional impairment. The individual should recognize the obsessions or compulsions as excessive or unreasonable. Obsessions are defined as persistent ideas, thoughts, impulses or images that are experienced as intrusive, inappropriate, and associated with significant anxiety or distress. Common obsessions include worries about having left a door unlocked, fears of contamination related to contact with others, or a need to have things in a specific order. Compulsions are repetitive behaviors such as hand washing, checking, and ordering, or mental acts such as counting or repeating words silently, that are performed to try to decrease the anxiety or stress associated with the obsessions. OCD has a prevalence of 2.3% in U.S. adults. The gold standard diagnostic instrument for OCD is the Yale-Brown Obsessive-Compulsive Scale. CBT with an exposure therapy element is the treatment of choice for OCD; SSRIs are the most effective pharmacotherapy, and should be used in cases where patients are resistant to CBT or do not improve sufficiently with CBT, as well as in cases that are more severe or in which a rapid response is critical. Higher doses are often needed than is the case for depression, and the dose may be escalated at 2-4 week intervals. Adjunctive use of antipsychotics has some evidence of benefit.

**SUMMARY**

Depression and anxiety are both extremely common in primary care and present special challenges to physicians who diagnose and treat them. Numerous medical and psychiatric conditions often complicate depression. Fortunately, the PHQ-9 and GAD-2 rapidly and easily facilitate initial diagnosis and subsequent monitoring of patients with depression and anxiety, respectively. A range of effective, well-tolerated medications are available to treat depression and anxiety disorders, narrowing the need for referral to a psychiatrist to patients who do not respond to medication or who have complicating features such as psychosis, suicidal ideation, or bipolar depression. While most patients can be effectively treated in the primary care setting, it is helpful to have psychiatric assistance when needed, particularly in light of competing demands in the primary care setting. Effectively treating these patients can reduce their utilization of medical services and improve their ability to return to a more productive life.

**Case Discussion**

Returning to the introductory case of a 35-year-old mother of three with complaints of fatigue, early morning awakening, and headache, these presenting symptoms might well be signs
of depression, with the early morning awakening being more specific for mood and anxiety disorders, especially depression, whereas the fatigue and headache are common symptoms associated with relatively broad differentials. Fatigue can be a presenting feature of such diverse conditions as heart failure, chronic pulmonary disease, renal failure, malignancy, infection, and anemia. Headache may be a primary problem—migraine or tension—or secondary to either local (brain tumor or infection) or some of the systemic conditions in the fatigue differential. Thus, a detailed history, including review of systems, and physical exam is necessary. Basic laboratory tests, including complete blood count and comprehensive metabolic panel, as well as thyroid function tests, should be obtained. However, more often than not, depression or an anxiety disorder will be the etiology of the symptoms, so screening for these should be incorporated in the initial evaluation, not merely diagnoses of exclusion to be considered after everything else is ruled out. She may well have mixed anxiety and depression, and if specific functional impairment is associated, treatment with an SSRI or referral to a mental health professional for CBT, are both reasonable options.
USEFUL REFERENCES

Depression

Anxiety


Table 1: *Criteria for Mood Disorders Other Than Major Depression*

**Bipolar I Disorder**

I. Current and/or previous history of a manic or mixed episode, defined as:

A. Manic episode
   1. A 1-week or longer period of abnormally and persistently elevated, expansive, or irritable mood
   2. During this period, three or more of the following symptoms have been persistent and significant:
      a) inflated self-esteem or grandiosity
      b) decreased need for sleep
      c) more talkative than usual or pressure to keep talking
      d) flight of ideas or feeling that thoughts are racing
      e) distractibility
      f) psychomotor agitation or increase in goal-directed activity
      g) excessive involvement in pleasurable activities that have a high potential for painful consequences
   3. Symptoms do not meet criteria for a mixed episode
   4. Function is markedly impaired
   5. Symptoms cannot be attributed to substance abuse, medication, or medical condition

B. Mixed episode
   1. Criteria are met for both a manic episode and a major depressive episode nearly every day for at least 1 week
   2. Function is markedly impaired
   3. Symptoms cannot be attributed to substance abuse, medication, or medical condition

II. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

III. The mood symptoms are not better accounted for by, or superimposed on, another diagnosis such as schizoaffective disorder or schizophrenia

IV. The mood symptoms are not due to a substance, medication, or medical condition
**Bipolar II Disorder**

I. As opposed to bipolar I, this is characterized not by mania but by a history of one or more hypomanic episodes, defined as:

   A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood

   B. During the period of disturbance, three or more of the following symptoms have been persistent and significant:
      a) inflated self-esteem or grandiosity
      b) decreased need for sleep
      c) more talkative than usual or pressure to keep talking
      d) flight of ideas or feeling that thoughts are racing
      e) distractibility
      f) psychomotor agitation or increase in goal-directed activity
      g) excessive involvement in pleasurable activities that have a high potential for painful consequences

   B. There is an unequivocal change in functioning associated with the episode, but it is not so marked as to require hospitalization or to severely impact social or occupational function, and psychosis is absent

   C. The change in mood and functional status is noticed by others

   D. The mood symptoms are not due to a substance, medication, or medical condition

**Persistent Depressive Disorder**
I. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years (or at least one year in a child or adolescent)

II. Presence, while depressed, of two or more of the following:

   A. poor appetite or overeating
   
   B. insomnia or hypersomnia
   
   C. low energy or fatigue
   
   D. low self-esteem
   
   E. poor concentration or difficulty making decisions
   
   F. feelings of hopelessness

III. During the 2-year period the individual has never been without the symptoms in criteria A and B for more than 2 months at a time

IV. No major depressive episode has been present during the first 2 years of the disturbance

V. There is no history of mania or hypomania
Table 2: Medications Associated with Depressive Symptoms

- Alcohol
- Benzodiazepines
- Corticosteroids
- Levodopa
- Neuroleptics
- Marijuana
- Stimulant, cocaine withdrawal
- Metaclopramide
- Methyldopa
- Opiates
- Propranolol
- Reserpine
- Isotretinoin

Table 3: Principles of Medication Use for Major Depression in Primary Care

- Document symptoms and associated difficulties
- Evaluate for preexisting or comorbid factors (bereavement, medical illness, medication, other psychiatric illness)
- Start single-agent antidepressant, titrating to therapeutic dose
- Assess compliance and initial response after 1-2 weeks, with re-assessment at 4-6 weeks to determine whether to change to different medicine (if no response), increase dose (if partial response), or continue current treatment (response)
- Follow up 4-6 weeks later to again re-assess compliance, need for increased dose, adding second agent, or changing medication
- For a single episode treat 4 to 9 months after symptom resolution; for two episodes, treat at least 4 to 9 months but consider prolonged treatment; for three or more episodes, treat for lifetime
- Refer patient to psychiatrist if patient is treatment resistant (poor response to adequate course of two or more agents)

Table 4: Indications for Referral of the Depressed Patient to a Psychiatrist

- Suicidal ideation or plans
- Bipolar disorder, either currently or prior episodes
- Psychotic features (delusions, hallucination, catatonia)
- Refractory to the antidepressants with which primary care physician feels comfortable
- Psychotherapy needed for optimal response (e.g., deep-seated family, interpersonal, or personality issues)
- Diagnostic uncertainty (e.g., atypical features; psychiatric or medical comorbidity; personality disorder)
Practice questions (and answers)

1. A 22-year-old female college student presents to her primary care physician for poor concentration ability and new concern for poor performance in her classes for the past month. She has been a straight “A” student until now, and endorses difficulty studying for her exams because she feels tired all the time. Her low energy level has contributed to her not wanting to participate in activities of previous interest. She has lost 5 lbs during this time, something she attributes to being stressed out. She is scared she might fail a class and has no one she can talk to at school.

What is the most likely etiology of this patient’s chief complaint?
A. Bipolar disorder
B. Major Depressive Disorder
C. Minor Depression
D. Persistent Depressive Disorder
E. Hypothyroidism

2. A 24-year-old medical student who recently began his clinical rotations comes to see you at the behest of your surgical colleague who is concerned about his wellbeing. The student recently began his surgical rotation, which he finds exhilarating. He reports staying up all hours of the night for the past week to prepare for surgical cases the next day. He feels it is extremely important for him to expand his knowledge base so he can impress his surgical mentors; much more important than sleep! During the appointment, he appears easily distractible and quite concerned that his surgical team needs his immediate assistance for a case right now. He endorses strong religious beliefs and states Jesus has sent him important messages. He feels he’s “at the top of his game” and recently bought an expensive car to celebrate his success. This comes in stark contrast to his description of his mood during the preceding 3 months, which he describes as his “low point”.

What is the most likely diagnosis in this patient?
A. Bipolar disorder
B. Major depressive disorder
C. Schizophrenia, paranoid type
D. Hyperthyroidism
E. Generalized Anxiety Disorder

3. A 39-year-old Army SFC reports to you for difficulty with sleep. He reports horrific, vivid nightmares for the past month from his most recent deployment to Afghanistan, during which he lost several close friends in an IED attack that he survived. He often
relives the experience in his dreams and has physically assaulted his spouse during one such nightmare. He has avoided going to the range with his unit, as the constant blasts and gunfire reminds him of the event and makes him feel jumpy. In further discussion he discloses his marriage is on the ropes and he feels isolated from the entire family, noting that he occasionally gets confrontational without perceivable reason.

What is the most likely diagnosis in this patient?
A. Insomnia
B. Post-Traumatic Stress Disorder
C. Acute Stress Reaction
D. Obsessive-Compulsive Disorder
E. Generalized Anxiety Disorder
Answers

1. The correct answer is major depressive disorder, B. She meets the DSM-V criteria for major depression. The patient is manifesting with > 4 weeks of poor sleep, anhedonia (lack of interest in previously pleasurable activities), decreased energy, poor concentration, and poor appetite. She is tearful during the visit and in many ways, appears to be reaching out for help. Her symptoms lack a manic quality. The chronicity and pattern are not congruent with minor depression or persistent depressive disorder. Hypothyroidism and depression can present similarly in some instances, however, the symptoms this patient endorses are not common for hyperthyroidism.

2. The correct answer is A, bipolar disorder. This patient is demonstrating classic symptoms of bipolar disorder. The syndrome is typified by periods of mania or hypomania and depression. This patient is currently in a manic episode, evidenced by a week of no sleep and extreme focus. Oftentimes the patients feel they are performing very well and do not appreciate the diagnosis until the depressive symptoms return. Mania is not a feature of major depressive disorder. Although he endorses strong religious affiliations, he does not have hallucinations common with schizophrenia. Hyperthyroidism can be associated with decreased sleep, however, is more commonly associated with tremor, palpitations and heat intolerance. This patient does not have features of debilitating anxiety, but rather extreme desire to perform well with his current mental focus; his clinical rotation.

3. The correct answer is B, post-traumatic stress disorder. According to DSM-V, PTSD is defined by the presence of two criteria from the traumatic event and presence of symptoms from 4 defined symptom clusters. The event must be a stressor due to experience and intense fear of horror or loss of control and manifest with intrusive recollections into memory, such as recurring images, thoughts, or dreams. The symptoms must include avoidant behaviors, hyper-arousal symptoms, and lasting more than a month. PTSD can be further classified as chronic or acute depending if the duration of qualifying symptoms persists beyond 3 months. In this case, insomnia does not account for all of this patient’s symptoms. An acute stress reaction may manifest with similar symptoms, however typically lasts for several days and does not last beyond a month’s duration. Generalized anxiety disorder is typified by symptoms of worry and apprehensive expectation. Obsessive-compulsive disorder is commonly focused or thematic and typified by behaviors to alleviate the anxiety associated with the obsession, resulting in compulsions that interfere with executive function.
Patient 1: A 62-year-old African-American man presents with three months of “food getting stuck” after he swallows. He initially had trouble swallowing solid foods such as steak, chicken, and bread but was able to continue eating these foods if he cut them into small pieces. His dysphagia worsened to the point where he stopped eating solid foods; he now eats only smoothies and milkshakes, but these are now becoming hard to swallow. When asked where food feels like it is sticking, he points to his suprasternal notch. His only medical problem is hypertension, which is treated with hydrochlorothiazide. His social history is notable for heavy alcohol and tobacco use. He has lost twenty pounds since his dysphagia began. Physical examination is notable for an ill, but non-toxic, appearing man.

Questions

1. What is the most likely diagnosis?

2. What are some of the risk factors for the development of this condition?

3. How would you work up this patient?

4. What “red flags” would prompt you to expedite this patient’s evaluation?

Patient 2: A 30 year-old man presents to the emergency room with food stuck in his esophagus for several hours. He was eating steak for dinner when the food got lodged in the region of the xiphoid process. He reports solid food dysphagia for several years with occasional food getting stuck, but he is usually able to drink liquids and wash the food down. He notes that he has been cutting food into smaller pieces and avoiding some foods to prevent food getting stuck. He has a history of asthma and seasonal allergies. He has been on a proton pump inhibitor for several months for intermittent heartburn. On physical exam, his vitals are normal. He appears somewhat uncomfortable and is spitting into a basin. The remainder of his exam is unremarkable.

Questions

1. How would you classify this patient’s dysphagia?

2. What is the most likely diagnosis?
3. How would you definitively establish the diagnosis?

4. What are your recommendations for treatment?

Objectives: At the end of this section you should be able to:

1) Differentiate oropharyngeal from esophageal dysphagia.
2) Gather historical data to further characterize esophageal dysphagia (e.g. solids only vs. solids and liquids, intermittent vs. progressive.)
3) Identify “red flags” in a patient presenting with dysphagia.
4) Recognize classic endoscopic and barium swallow x-ray findings in major categories of esophageal disease: Esophageal cancer, benign peptic stricture, eosinophilic esophagitis, and achalasia.
5) Apply tests, such as barium swallow, upper endoscopy, esophageal manometry or 24 hour pH monitoring, in a patient with dysphagia.
6) Compare and contrast the most likely causes of painful swallowing (odynophagia), such as pill esophagitis, Candida esophagitis, and HSV/CMV esophagitis, and know which conditions to suspect in immunocompromised patients.

Overview:
This ICR topic, illustrates the use of heuristics, key findings, as well as a well-established schema for ascertaining the cause of dysphagia. The approach to other esophageal disorders is also discussed using the key finding approach. The emphasis of this topic will be anatomy, pathophysiology and the use of this schema to help you diagnose patients presenting with dysphagia.
Definitions:

**Dysphagia** - Difficulty in swallowing or the perception that the solid food/liquid bolus is being hindered in its normal passage from the mouth to the stomach.

**Odynophagia** - Term utilized when the act of swallowing induces pain (painful swallowing)

**GERD** (Gastroesophageal Reflux Disease) - Term referring to a condition characterized by symptoms or findings resulting from reflux of gastric contents (usually acid) up in to the esophagus.

I. Anatomy of the Esophagus

Swallowing is a voluntary event which initiates involuntary/automatic responses. Following transfer of the bolus to the posterior oral cavity, further transfer of the bolus from the oro-pharynx into the cervical portion of the esophagus and then propulsion of the bolus down the esophageal body into the stomach is mediated by involuntary responses. Normally, there is no perception of the transit of the bolus down the esophagus and into the stomach.

A. Length - About 20-25 cm from the cricopharyngeous muscle to the stomach.

B. Musculature

1. Striated muscle in the upper 1/3 of the esophagus
2. Smooth muscle in the lower 2/3 of the esophagus

It is important to understand that the upper esophagus is composed of striated muscle and that this differs from the composition of the lower esophagus. Disorders of *striated muscle*, such as amyotrophic lateral sclerosis, will affect the upper esophagus and interfere with transfer of the bolus through the pharynx and upper esophagus. Disorders of *smooth muscle*, such as scleroderma, will affect the lower esophagus.

C. Sphincters

1. **Cricopharyngeal sphincter**- Also known as the upper esophageal sphincter or UES. If this sphincter does not relax when you swallow, then a sensation of liquid through the nose will soon follow.

2. **Lower esophageal sphincter (LES)** - The zone of high pressure located at the distal end of the esophagus and prevents reflux of gastric contents back up into the esophagus. The resting LES pressure is 10-25 mm Hg.

D. Epithelial lining- The mucosa or epithelial lining of the esophagus is squamous. This differs from the stomach, which has a columnar cell lining. The squamous mucosa joins the columnar mucosa at the junction of the stomach and esophagus (GE or gastro-esophageal junction). This junction can be clearly identified at endoscopy of the esophagus due to the different colors of these two mucosal linings.
II. Physiology of Swallowing

A. To accommodate the bolus in the oral cavity, the tongue forms a groove in the mid line that complements the high arched hard palate in creating a space. The teeth masticate the bolus into small pieces. Sensation in the hard palate determines when the pieces are small enough to swallow.

B. During the act of swallowing, the tongue moves posterior and acts as a piston to ram the bolus into the oropharynx. At this time, the soft palate closes off the nasopharynx to prevent regurgitation. The pharyngeal constrictors then propel the bolus through the cricopharyngeal sphincter (UES) which reciprocally relaxes to permit the bolus to enter the esophagus.

C. To prevent pulmonary aspiration while the bolus passes around the larynx and into the cervical esophagus via the pyriform sinuses, the larynx moves upward and forward. Both the false and true vocal cords approximate, respiration stops, and the epiglottis moves forward to protect the airway.

D. The contraction wave that began with the pharyngeal constrictor muscles continues down the body of the esophagus and is termed the primary peristaltic contraction wave. Solid and liquid particles are propelled through the esophagus by these waves although in the upright position, liquids will fall through the esophagus and into the stomach often preceding the peristaltic wave that is generated with the swallow. It takes approximately 8-10 seconds for the bolus to traverse the esophagus (2-3 cm/sec wave velocity). If the bolus fails to transmit through the esophagus during the primary peristalsis, then the presence of the bolus will initiate a secondary peristaltic contraction wave that clears the solid. This secondary peristaltic contraction occurs in the absence of a swallow. A secondary peristaltic wave will also be initiated if a volume of gastric contents is refluxed up into the esophagus. These peristaltic waves are generated to clear the esophagus and are not perceived.

E. The LES begins to relax immediately after the UES relaxation and remains relaxed for approximately 7 seconds so that the primary or secondary esophageal contractions can propel the bolus into the stomach. The fundus of the stomach accommodates the arrival of the bolus by receptive relaxation.

F. The LES regains its tone after the primary or secondary peristaltic contraction wave travels through the LES area.
III. Esophageal vs. Oropharyngeal Dysphagia

The two major types of dysphagia are **esophageal dysphagia** and **oropharyngeal dysphagia** (also known as pre-esophageal or transfer dysphagia). *The first major task when evaluating a patient with dysphagia is to determine if they are experiencing esophageal or oropharyngeal dysphagia.*

A. Oropharyngeal dysphagia. As noted above, the act of transferring food or liquids from the oropharynx to the esophagus is a complicated procedure. Impairment of the muscles that perform this process or the neurologic elements that coordinate it may result in oropharyngeal dysphagia. Patients with oropharyngeal dysphagia typically have difficulty swallowing liquids and have coughing, choking or nasal regurgitation after attempting to swallow. Problems occur while swallowing or immediately after swallowing. If asked to localize their symptoms, patients with oropharyngeal dysphagia with typically identify the anterior cervical area above the suprasternal notch.

1. Causes of oropharyngeal dysphagia. As seen below, oropharyngeal dysphagia is often one manifestation of a more widespread neurologic disease or part a systemic disease process.
   
   a. Neurologic lesions (such as stroke, cranial neuropathies, multiple sclerosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease).

   b. Neuromuscular disease (such as myasthenia gravis)

   c. Striated muscle disease (such as dermatomyositis, muscular dystrophy, or myotonic dystrophy).

2. The diagnosis of oropharyngeal dysphagia can be confirmed with a modified barium swallow, which is a fluoroscopic examination that provides real-time views of the swallowing apparatus. This examination is typically performed by a speech pathologist.

3. Treatment of oropharyngeal dysphagia may include a special thickened diet, exercises to improve the patient’s swallowing, or a feeding tube. Speech pathologists can help plan the patient’s treatment.

B. Esophageal dysphagia is difficulty swallowing after the food bolus has entered the esophagus. Patients may describe this as “food stuck,” “food won't go down,” “food gets hung up,” or “food gets caught.” Since patients are able to initiate and complete the oropharyngeal phase of swallowing, there is a definable time interval (2-7 seconds) before the onset of the sensation of dysphagia. The patients may experience an
impact discomfort or pain associated with the sudden stoppage or hang up of the bolus. This impact discomfort will resolve when the bolus passes or is regurgitated. Coughing, choking, or nasal regurgitation is typically absent in patients with esophageal dysphagia. Additional historical data important in the evaluation of esophageal dysphagia will be discussed below.

The patient in our introductory case initially had problems swallowing solid food and felt that food was getting stuck when he swallowed. His symptoms are most consistent with esophageal dysphagia.

IV. Historical Information in Patients with Esophageal Dysphagia

A. What types of food causes symptoms? Try to ascertain if the patient has problems only with solid food or if symptoms occur with both solids and liquids. Some patients may complain of symptoms only with specific foods, such as steak. It is also important to ask patients if they cut their food into smaller pieces or even modify their diet to soft mechanical food. With modification of diet, patients may no longer have dysphagia. An anatomic lesion (such as an esophageal ring or web) typically causes problems only with solid food whereas an esophageal motor disorder will impede both liquids and solids.

B. Are the symptoms intermittent or continuous/progressive? A narrowing or stricture of the esophagus will first impede solids and then, as the lumen becomes narrower, will impede liquids. Intermittent symptoms are more often seen in benign esophageal strictures. An individual will not usually experience dysphagia until the diameter of the esophageal lumen is reduced by 2/3 of the normal. At approximately 12-13mm in diameter, patients will usually experience solid food dysphagia.

C. Where does it feel like the food is getting stuck? The area of the sensation (where the food is sticking) will generally correspond to the area of pathology or be located proximal (above) the area of pathology. For example, a patient who has a stricture at the GE junction will feel food hanging up in the lower chest or anywhere above (such as in the suprasternal notch). A patient with an upper esophageal stricture will sense the "hang up" in the upper chest or at the cricoid, but will not sense it lower than the area of pathology.

D. What is the timing between swallowing and the onset of symptoms?

E. Determine the manner of onset (e.g. insidious versus a specific date).

F. Are other esophageal symptoms such as heartburn, regurgitation, odynophagia, or chest pain present?

G. What associated symptoms (such as hoarseness, sore throat, bronchitis, chronic cough,
recurrent pneumonia, and weight loss) are present?

H. Review the patient’s overall medical history for conditions or risk factors that may predispose the patient to esophageal disease (“assess what they are at risk for”). Examples include: Heavy alcohol use and smoking (esophageal cancer), caustic (lye) ingestion (esophageal stricture), medications (some drugs can induce a caustic or burn injury to the esophagus), surgeries (prior trachea-esophageal fistula repair may result in a stricture). Also determine whether the patient has a strong history of allergies (food or otherwise) as a child or as an adult (patient with a strong atopic history may be at risk for eosinophilic esophagitis).

V: Causes of Esophageal Dysphagia:

A: Intermittent solid food dysphagia

1. Schatzki's ring - A 360 degree web-like stricture located at the GE junction and arising from connective tissue is known as a Schatzki's ring. It is also known as a B ring. The cause is not entirely clear, however chronic reflux of acid may play a role in the development of this constriction. The patient may not have any symptoms of GERD. The same sized bolus characteristically causes intermittent dysphagia (may occur once a meal to once a month or longer). Esophageal dilation is the treatment of choice followed by acid suppressive medications.

2. Eosinophilic esophagitis (EoE): In this category of patients, dysphagia is usually intermittent but may become progressive. The patients may be children or adults and often have coexisting allergic history in more than half of patients. For adults, the major complaint is solid food dysphagia and food impactions. Some patients have a concomitant history of GERD.

- Endoscopic findings in patients with eosinophilic esophagitis include multiple rings (55%), linear furrows (33%), narrow esophagus (10%), and esophageal strictures (38%); however the esophageal mucosa may be normal in approximately 10% of patients. The major diagnostic criteria for eosinophilic esophagitis is >15 eosinophils per high power field (HPF) on biopsies of the esophageal mucosa which have not responded to a 6-8 week course of acid suppressive medications (PPIs).

- Treatment of this disorder includes elemental diets (children) and food elimination diets (most commonly milk, wheat, eggs, soy, nuts, and shellfish) in both children and adults. Topical corticosteroids (fluticasone, budesonide) are effective in inducing a histologic and clinical response in many patients, however symptoms may reoccur following cessation of the steroids. Systemic steroids may be used in refractory cases. PPIs help control symptoms of many patients with EoE. If strictures develop, esophageal dilation is very effective in improving symptoms of dysphagia.
3. Other causes of this type of dysphagia include:
   - Benign esophageal tumors such as a leiomyoma (smooth muscle tumor)
   - Vascular extrinsic compression (dysphagia aortica, dysphagia lusoria, prominent atria)
   - Chronic mediastinal inflammatory diseases such as sarcoidosis, TB, and histoplasmosis

B. Progressive solid food dysphagia

1. **Benign peptic strictures** secondary to GERD. Heartburn and other symptoms of reflux disease are often present. The dysphagia progresses over time and the patient must cut food into smaller and smaller pieces. Rarely will the dysphagia get so severe that the patient complains of liquid dysphagia. Generally, the dysphagia has been present for more than a year.

2. **Malignant esophageal strictures:** The patient usually has an insidious but progressive onset of dysphagia (eventually the patient will also complain of liquid dysphagia). Heartburn is usually not a complaint elicited from these patients. The patient will usually experience progressive weight loss, which should be a red flag that prompts an expedited evaluation.

The patient in our introductory case has esophageal dysphagia with began with solids and has progressed to dysphagia with both solids and liquids. With his heavy alcohol use, tobacco use, and weight loss, there is a strong concern for esophageal cancer. This patient needs an expedited evaluation.

C. **Solid and liquid dysphagia:** Patients that initially experience esophageal dysphagia to both solids and liquids generally have an **esophageal motor disorder.** Esophageal motor disorders include:

1. **Achalasia** - This disorder is characterized by: 1) the lack of or incomplete relaxation of the LES with swallowing. 2) a complete loss of esophageal peristalsis. 3) The LES pressure may be normal or high. This phenomenon causes a functional esophageal obstruction that leads to retention of a meal in the esophagus. Liquids and solids accumulate in the esophagus. Fermentation of the food in the esophagus may cause reflux symptoms and this disorder may be confused with GERD. A portion of the esophageal contents eventually pass into the stomach as the swallowed food increases the pressure column of the retained food and overcomes the LES pressure. Over time, the esophagus eventually dilates. Patients will often present with chest pain, weight loss and dysphagia.

   − **Epidemiology:** Disorder of young and middle age adults but can affect any age.
   − **Pathophysiology:** Destruction of ganglion cells for an unknown reason.
   − **Radiology:** Classically, a barium swallow will show a "bird's beak" pattern of the distal esophagus with esophageal body dilation.
   − **Treatment:** Smooth muscle relaxants such as nitrates and calcium channel blockers and endoscopic injection of Botulinin toxin into the area of the LES may be temporarily effective in some patients. Pneumatic dilation and surgical myotomy are the most effective treatment
Differential diagnosis: Cancer located in the fundus of the stomach can present with an achalasia-like appearance when the neoplasm infiltrates up the esophageal wall and destroys the neural elements. This is known as pseudo-achalasia. Chagas disease is also on the differential in patients who have travelled to areas endemic for this disease.

2. **Diffuse Esophageal Spasm** - A rare esophageal motility disorder that is characterized by an increase and duration of peristaltic and non-peristaltic contractions of the esophageal body. These contractions frequently correlate with episodes of severe chest pain. The chest pain can be similar to angina pectoris. Eating fast and emotional stress may intensify this disorder. Despite severe dysphagia and chest pain experienced by these patients, they generally experience a stable course over time and do not lose weight.

3. **Scleroderma** - This disorder of smooth muscle results in decreased or absence of the LES pressure and absence of peristalsis in the distal 2/3 esophagus. Thus, the patients frequently reflux (because there is no LES pressure to keep the gastric contents from migrating up the esophagus) and then the esophagus is unable to effectively clear the refluxed material (because peristalsis is absent). This results in prolonged gastric acid exposure to the lower esophagus and severe GERD. These patients often experience esophageal strictures. Many patients also have Barrett’s esophagus. Treatment is to completely suppress gastric acid production. This therapy will not prevent reflux but will keep the refluxed material from injuring the esophageal mucosa. Scleroderma is rarely seen in men.

4. **Chagas Disease** - Trypanosoma cruzi invades the ganglion cells of the esophagus and causes and achalasia-like disorder. This disorder should be considered in travelers and immigrants from endemic areas. The patients may also have megacolon, megaureters, and congestive heart failure.

**VI: Odynophagia**

Odynophagia is defined as pain on swallowing. It is important to differentiate from dysphagia since the diagnostic considerations are entirely different. Generally, odynophagia is secondary to mucosal injury or inflammation (usually an infection or caustic injury). Odynophagia can be so severe that the patient will drool saliva because of fear of swallowing. Important causes of odynophagia include:

1. **Infections** - Occurs primarily in immunocompromised patients (AIDS, malignancy, post chemotherapy)
   
   a. Candida fungal infection - The presence of oral candidiasis (thrush) does not establish the presence of esophageal candidiasis.
b. Herpes Simplex Virus (HSV).

C. Cytomegalovirus (CMV).

2. Noninfectious Causes

a. Pill induced injury- Some medications are caustic to the esophageal mucosa if the pill does not rapidly transit the esophagus (e.g. tetracycline, aspirin, quinidine, vitamin C, multivitamin, bisphosphonates, and potassium). Patients who sustain a pill injury are generally elderly, took the pill with no or insufficient fluids and/or immediately went to sleep after taking the pill.

b. Caustic injury- Lye injury

c. Idiopathic esophageal ulceration- Found in HIV disease.

VII: Gastroesophageal Reflux Disease (GERD). Approximately 45% of adult Americans will experience a symptom related to reflux (usually heartburn) at least once a month. As many as 7% of adult Americans have a daily occurrence of reflux symptoms. Thus, gastroesophageal reflux is one of the most common GI problems that you will encounter. Gastroesophageal reflux is a normal physiologic event and typically occurs transiently during or after eating. GERD is the condition where the exposure of the esophagus to gastric contents is greater than normal. Histologically, GERD also has eosinophils present, but usually less than those seen in eosinophilic esophagitis.

1. Nomenclature:

Heartburn/Pyrosis - Refers to the sensation of retrosternal burning. It is suspected that this sensation is initiated by irritation of esophageal nerve fibers by gastric acid.

Reflux esophagitis - Refers to inflammation of the esophageal mucosa that can be identified on endoscopy, barium swallow, or on endoscopic biopsies of the esophageal mucosa. The inflammation can be varying in severity: erythema, erosions, ulcers, and/or strictures.

Barrett's Esophagus - Condition in which the distal esophagus is lined by columnar epithelium, which has intestinal features to include the presence of goblet cells. Remember, the esophagus is normally lined by squamous epithelium. This abnormal columnarization of the esophagus can be present just at the GE junction or can extend up the esophagus at any length. It is a complication of reflux and is a risk factor for the development of adenocarcinoma of the esophagus. The condition is asymptomatic except for reflux symptoms and is typically diagnosed by upper endoscopy and biopsy.
2. **Pathophysiology**

The injury to the esophageal mucosa is multifactorial. Traditionally, the etiology for pathologic reflux has focused on decreased lower esophageal sphincter (LES) pressure, which allows for easy reflux of gastric contents into the esophagus and results in excessive acid exposure and mucosal damage. However, transient relaxations of the LES (relaxations of the LES that are not associated with a swallow; resting LES pressure is normal) have also been implicated as an important cause of GERD. In addition, alkaline reflux, consisting of pancreatic juices and bile may also be an important factor in causing esophageal inflammation. Delayed gastric emptying, the presence of a hiatal hernia, and decreased volume of saliva production also contribute to GERD.

3. **Symptoms**

Heartburn, chest pain, excessive salivation, and halitosis. The sensation of dysphagia may occur with esophagitis and resolves with treatment. Strictures of the distal esophagus will cause dysphagia when the luminal diameter of the esophagus approaches 12 mm. Odynophagia is usually not a symptom of GERD.

Extra-esophageal Symptoms: ENT and pulmonary specialists have recognized that GERD can manifest with hoarseness, globus, aspiration pneumonia, sore throat, sinusitis, asthma, and chronic cough. The mechanism of injury is by direct contact of the refluxed gastric juices and neurogenic reflexes via nociceptive receptors in the distal esophagus.

4. **Evaluation**

5. Many methods are available for the diagnosis of GERD to include:

   **Physical Exam**: Findings are limited in GERD, but erosion of the dental enamel may be seen in some patients.

   **Barium Swallow**: Radiology study shows gross esophageal motor function and mucosal detail. May also note esophageal strictures that are missed on EGD as newer endoscopes have smaller diameters allowing for passage thru narrow strictures.

   **Upper Endoscopy**: Fiberoptic endoscopic evaluation of the esophagus that allows for direct visual evaluation of the esophagus, stomach and duodenum. Endoscopy also allows for sampling/biopsy of the mucosa for microscopic evaluation. Endoscopic evaluation does not assess motor function of the esophagus. Upper endoscopy is the procedure of choice for the evaluation of odynophagia, dysphagia or other disorders in which mucosal inflammation or carcinoma is suspected.

   **Esophageal Manometry**: Manometry is performed by passing a small tube with pressure sensors into the esophagus. LES pressure, LES relaxation, and esophageal body pressures can be obtained at rest and with swallowing. Esophageal manometry is the procedure of choice to evaluate esophageal peristalsis and to diagnosis esophageal motor disorders.
Prolonged pH monitoring (usually 24 hour measurement). A pH wire catheter is passed nasally into the esophagus and placed above the GE junction. Continuous pH monitoring is recorded on a device (size of a Sony Walkman) that is attached to the catheter. This examination is useful to quantify reflux, to evaluate reflux in relationship to activity (upright and supine positions,) and to confirm the presence of reflux in patients with atypical chest pain. 24 hour pH testing is the gold standard for GERD diagnosis.

Recent advances in technology allow for a pH probe to be pinned in the esophagus (Bravo capsule) so that a catheter protruding from the nose is no longer needed. The capsule sends radio frequency signals to a recorder placed on a belt around the patient’s abdomen, then detaches from the esophagus after about 3-4 days and passes throughout the GI tract without having to be retrieved.

Impedance Monitoring: This is a catheter device which has both a pH sensor for monitoring acid reflux and an impedance sensor that measures liquids or gas entering the esophagus. The advantage of this device is that it allows for the measurement of weakly acid contents (pH >4) into the esophagus. Typically, this device is used to determine whether symptoms such as a chronic cough or hoarseness relate to weakly acid reflux in patients taking proton pump inhibitors (PPIs) which will raise intragastric pH to >4 for 12-15 hours in the day. A pH probe is typically most accurate in measuring pH<4 and may thus miss weakly acid reflux.

5. Treatment

Treatment depends upon the severity of symptoms and the extent of esophagitis. Patients with occasional heartburn (majority of people with GERD) usually get prompt relief with antacids (taken as needed) and lifestyle changes.

a. Simple anti-reflux lifestyle changes
   - Discontinue smoking
   - Weight reduction if overweight
   - Avoid large meals, late suppers, and evening snacks
   - Elevate the head of the bed four to six inches (with blocks under the front bedposts or pillows).
   - Avoid alcohol, peppermint, fatty foods, spicy foods, chocolate, and coffee.

b. Medical therapy for GERD:

   Antacids (e.g., Mylanta© and Tums©) - Convenient for patients who have mild symptoms. Their use becomes impractical if frequent use is necessary.

   Alginic Acid (Gaviscon)- When this medication comes in contact with acid, it forms a floating gel on top of the gastric contents and provides a physical barrier to reflux.

   H2 Receptor Antagonists (cimetidine, ranitidine, famotidine) - Fast becoming one of the most popular over the counter medications, the H2 blockers are effective for mild-moderate GERD. These medications usually require twice a day dosing. In severe reflux esophagitis,
the healing response rates are only around 50%. Higher doses are required for healing of severe esophagitis than what is required for peptic ulcer disease.

Proton pump inhibitors (omeprazole, lansoprazole, dexlansoprazole, rabeprazole, pantoprazole, esomeprazole): These agents are the most potent acid suppressive drugs and are effective for the treatment of moderate-severe reflux esophagitis. Because these medications are often initiated empirically to manage GERD, it is important to recognize several important drawbacks. Several proton pump inhibitors have been found to have important interactions with other medications (e.g. reduced hepatic conversion of the platelet inhibitor pro-drug clopidogrel to the active form). Also, several medications in this class have been associated with pneumonia (both hospital- and community-acquired) and increased risk for *Clostridium difficile* infections.

c. **Surgical therapy for GERD:** The end-result of anti-reflux surgery is to increase the lower esophageal sphincter pressure. The distal esophagus is wrapped utilizing portions of the gastric body. This procedure can be performed by laparoscopy. The most common operation/technique is known as a laparoscopic Nissen fundoplication. A 24 hour pH study and esophageal manometry should always be performed prior to surgery to ensure that abnormal esophageal reflux is present and that there is no underlying esophageal motor disorder. Candidates for surgical therapy of GERD include patients who experience complications (e.g. strictures, aspiration pneumonia) or possibly those who require chronic high dose PPIs and who would rather not take a pill the rest of their life.

6. **Other Esophageal Disorders:**

A. **Globus hystericus:** It is the sensation described as "a lump in the throat" which is localized to the anterior cervical region but for which no anatomical basis can be established. In contrast to dysphagia, globus sensation is constantly present and does not interfere with swallowing. In fact, globus hystericus is often relieved with swallowing of liquids and solids. Globus hystericus is often exacerbated by stress. Patients with globus have a high prevalence of anxiety and depressive symptoms as well as obsessive traits. Before a diagnosis of globus hystericus is made, patients should undergo evaluation since esophageal reflux, hypertensive upper esophageal sphincter, and goiter have been reported as presenting with globus sensation.

B. **Zenker's Diverticulum:** Pharyngoesophageal diverticulum formed by the protrusion of posterior hypopharyngeal mucosa between the oblique fibers of the cricopharyngeus. The diverticulum is located proximal to the start of the esophagus. Patients are usually older than 50 and complain of dysphagia, bad breath and regurgitation of undigested food.

**VII: Returning to our patients...** As we previously mentioned, the first patient had progressive solid food dysphagia and there was a strong concern for esophageal cancer. Upper endoscopy showed a large mass in the mid-esophagus. Biopsies were positive for squamous cell carcinoma. A
CT scan of the chest, abdomen, and pelvis showed no evidence of metastatic disease and an endoscopic ultrasound is planned to determine if the patient’s tumor is resectable.

Our second patient has intermittent dysphagia to solids which has been progressive. He presents with a food impaction secondary to a stricture from eosinophilic esophagitis. His age and coexisting history of atopic disorders are clues to this diagnosis. Diagnosis is established by esophageal biopsy and finding dense eosinophils (>15 eos/hpf) despite being on a PPI for at least 6-8 weeks. His stricture should be dilated, which will immediately improve his dysphagia and he should be prescribed a topical steroid. Alternatively, elimination of a potential food allergen may be performed.

**Pediatric considerations in the approach to dysphagia....your next patient**

*J.B. is a previously healthy 6 month old boy that you have seen for all of his health maintenance visits. As you flip through the chart, you are reminded that J.B. was the product of a full term, spontaneous vaginal delivery without any complications. At his previous visits, he was noted to be healthy and developing appropriately. You noted at both the 2 month and 4 month visits that the mother complained that J.B. ‘spit up’ quite a bit. Since he had been gaining weight appropriately and was otherwise ‘a happy baby,’ you reassured mom that spitting up is exceedingly common (seen in >50% of healthy infants) and that you would follow up with her again at this visit. Today, however, she explains that J.B.’s appetite seems to have decreased over the last few weeks and he is often fussy around feeds. He even seems to occasionally refuse the breast or bottle. Mom is also concerned that he doesn’t seem to be putting on weight like he had been before. There is no family history of any GI disease, his immunizations are up to date, and he has otherwise been well with no signs or symptoms of illness including fever, upper respiratory infections, or vomiting and diarrhea. In fact, the mother adds, his actual ‘spitting up’ seems to be less than before.*

Dysphagia is a relatively uncommon complaint in children. Moreover, the symptoms of dysphagia can be very difficult to elicit. Young children may have trouble in describing and characterizing their difficulty swallowing. Infants and toddlers will often just refuse to eat or become fussy or irritable around mealtimes. While primary motility disorders occur infrequently in the pediatric population, a careful history will alert you to conditions that might predispose a child to dysphagia. For example, repair of a Tracheal-Esophageal Fistula (TEF) [Tracheo-esophageal fistulas or esophageal atresia are seen in 1:3000 live births and approximately 50% of infants with this condition have associated anomalies, the most common being VATER or VACTERAL (Vertebral, Anorectal, Cardiac, Renal, Radial, and Limb)] often results in permanent dysmotility of the lower esophagus and may present with symptoms of motor dysfunction, obstruction, or both. Children with underlying neuromuscular disorders may also present with dysphagia. For example, children with cerebral palsy or muscular dystrophy often have difficulty with coordinated swallowing. Children with less common diseases like dermatomyositis, myasthenia gravis, and scleroderma may also present with dysphagia. Other congenital defects (vascular ring or tracheobronchial remnant) should also be considered in a child with obstructive symptoms. Although rare in children under 4 years old, adolescents may have achalasia and will have the signs and symptoms consistent with an adult presentation of this condition. There are often no specific physical exam findings in infants and children with dysphagia. Further investigational studies (i.e. barium
swallow, upper endoscopy, and esophageal manometry) can be conducted in the same fashion as they would for adult patients.

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux (GER) is defined as passive reflux of gastric contents upward into the esophagus or oropharynx. Ask any parent, and they will quickly tell you that most infants experience some degree of GER. In fact, ‘spitting up’ is normal in infants younger than 8 to 12 months, and nearly half of all infants experience it. No specific test is needed to diagnose reflux—when the breast milk or formula that an infant previously ingested ends up on the lap or the shoulder of the caregiver, the diagnosis is obvious. The combination of more solid foods, spending more time upright, and the development of a more compliant stomach means most infants outgrow this physiologic GER by 9 to 12 months. In contrast, gastro-esophageal reflux disease (GERD) occurs when there are pathologic findings that result from the reflux. Infants obviously cannot complain of ‘heartburn’ and their symptoms may be very non-specific. Infants may refuse to eat or become fussy around meal times and often will not gain weight appropriately. Special attention needs to be paid to other, perhaps subtle signs including coughing and wheezing that can be secondary to reflux. Sandifer syndrome—opisthotonos (a posture in which the head and the heels are bent backward and the body bowed forward), and other abnormal head movements—is also associated with reflux. If you suspect GERD, a barium swallow or upper GI series helps to rule out gastric outlet obstruction or other anatomic contributors to GER. A pH probe can also be used to monitor the esophageal pH. The treatment of GERD is similar to adults and is aimed at reducing the acidity of the gastric contents refluxing into the esophagus. H2 receptor antagonists or proton-pump inhibitors are considered first line, and if needed, prokinetic drugs like metoclopramide can be considered. If severe symptoms persist despite maximum medical therapy, surgical intervention (Nissen fundoplication) may be necessary.

Your physical exam of J.B. is unremarkable, but you note that his weight, which had previously been tracking along the 75% percentile, has dropped to below the 50% while his height remains unchanged. While in the exam room, you witness J.B. attempt to take a bottle and he seemed very reluctant to eat. He also assumed an odd posture with his head arched back and his stomach bowed out. Given all of these concerning findings, you order an upper GI series which shows severe reflux into the oropharynx. You discuss these findings with the parents and start him on a proton-pump inhibitor. In a phone call follow up two weeks later, the parents report he is a like a new child—he is back to eating everything in sight, his demeanor is much improved, and mom and dad couldn’t be happier. When you see J.B. back for his 9 month visit, his weight has returned to the 75%. You recall that most infants outgrow their reflux by 12 months, and elect to continue J.B. on medicine until he turns a year, at which time you will try him off medicines to see if his symptoms return.
Practice questions (and answers):

1. A 60 year-old male presents with food getting stuck in his throat. He describes symptoms as beginning shortly after eating solid foods and that he has had to cut his food into smaller pieces over the past several months as his symptoms seem to be getting worse. He does not report difficulty with swallowing liquids. If you were considering a diagnosis of peptic stricture and you learned that he was diagnosed with iron deficiency anemia 3 months ago, this diagnosis becomes?

   a. More likely
   b. Less likely
   c. Neither much more or less likely

2. A 60 year-old male presents with food getting stuck in his throat. He describes symptoms as beginning shortly after eating solid foods and that he has had to cut his food into smaller pieces over the past several months as his symptoms seem to be getting worse. He also reports difficulty with swallowing liquids over this time period. If you were considering a diagnosis of achalasia and you learned that his LES pressure is elevated, this diagnosis becomes?

   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely

3. Which of the following is more likely to present with transfer dysphagia?

   a. Cerebrovascular accident
   b. Cervical web
   c. Zenker’s diverticulum
   d. Diffuse esophageal spasm

4. A 36 year old man presents with dysphagia to solids and liquids for several months. Occasionally, he regurgitates undigested parts of his meals. He undergoes a barium esophagram which shows a sigmoid appearance to the esophagus. A manometry is performed and confirms your suspicion. All of the following would be treatment options except?

   a. Trial of nitrates
   b. Botox injection into the LES
   c. Pneumatic dilatation
   d. Referral for Heller myotomy
   e. Trial of PPI therapy
**Answers:**

1. More likely. In the setting of anemia (especially iron deficiency anemia) and dysphagia, you need to consider malignancy.

2. Much more likely. This is a component of the definition of achalasia.

3. The answer is cerebrovascular accident. Transfer dysphagia is otherwise known as oropharyngeal dysphagia, which is difficultly transferring the food bolus from the mouth to the oropharynx, which can occur secondary to neurologic conditions such as a stroke. Cervical web is a structural abnormality which occurs in the proximal esophagus and is a potential cause of transit dysphagia. Zenker’s diverticulum is a pouch which forms at the upper esophageal sphincter in older individuals. Food can get stuck in the diverticulum, however the transfer process of food is functional. Diffuse esophageal spasm is a rare motor disorder of the esophagus and can present with chest pain and dysphagia.

4. The answer is trial of PPIs. The patient has a history of solid and liquid food dysphagia along with the findings on barium esophagram which suggest a diagnosis of achalasia. This is confirmed on esophageal manometry. Many options exist for management. Medications such as nitrates and calcium channel blockers are smooth muscle relaxants and may be tried, however are not usually very effective long-term. Similarly, injection of botox into the lower esophageal sphincter will relax the esophagus and improve emptying, but again this is effective short-term. More definitive therapies include pneumatic dilation of the esophagus and Heller myotomy. PPIs do not have much of a role in the management of achalasia.
ICR: Acute and Chronic Diarrhea

John Horwhat, MD

Patient 1: You are stationed at EMF Kuwait. A 38-year-old black Army First Sergeant comes to your clinic. He recently deployed with a civil services unit, a “hearts and minds” type of combined force that traveled through parts of East Africa in support of local government and humanitarian efforts offering consultation on anything from force security to civil engineering projects to public health services. During the trip he subsisted mostly on the local economy. He has been back in Kuwait now for 2 months.

Now he complains of daily loose to watery bowel movements, without blood or pus, which are typically brown or greenish in color to almost clear water. The symptoms began during his deployment. He reports that “everyone had the runs” at some point during the trip, but is unsure if anyone else is having ongoing symptoms as he is. He also complains of mild crampy abdominal pain, but denies fever or chills, night sweats, tenesmus, or nocturnal BMs. He reports an unintended weight loss of 6 lbs during the past 3 months of continued diarrhea.

On exam, he is afebrile, and vital signs are stable. He is well appearing but thin. Cardiac and pulmonary exams are unrevealing and abdominal exam shows active bowel sounds and no guarding or tenderness to palpation. There is no hepatosplenomegaly and no ascites.

Patient 2: A 45 year-old woman presents to the emergency room following a few episodes of rectal bleeding which began after the sudden onset of cramping left sided abdominal pain. She has been to the bathroom several times with fecal urgency, however only has small bowel movements, all of which tinge the entire toilet bowl bright red. She has no changes in her diet and rarely eats outside of home. Her medical history is notable for systemic lupus erythematosis. Her only medications are oral contraceptives and occasionally sumatriptan for migraine headaches. Her examination shows normal vital signs and a mildly tender abdomen around the umbilicus. Rectal exam reveals normal tone and bright red blood on the gloved finger. Her labs show a mild leukocytosis and a slight drop in hemoglobin. A CT of the abdomen is ordered and demonstrates circumferential thickening of bowel in the region of the sigmoid colon.

Objectives: At the end of this session, students will be able to:

1) Define the terms acute and chronic diarrhea

2) Understand that diarrhea can be classified and approached in multiple different ways: by time course (acute vs. chronic), volume (large vs. small), pathophysiology (secretory vs. osmotic), epidemiology (epidemic vs. travel-related vs. immunosuppression-related) and stool characteristics (watery vs. fatty vs. inflammatory).

3) Recognize key clinical clues (history, PE, labs) to assist in the evaluation of acute and chronic diarrhea (see also flow charts in lecture slides)

4) Understand the rational, cost-effective use of tests to help classify/diagnose the etiology of diarrhea: e.g. fecal leukocytes, cultures, O and P, Clostridium difficile testing, endoscopy, osmotic gap
Overview

Diarrheal illness is one of the most common outpatient illnesses in the world and a common clinical dilemma faced by gastroenterologists, internists and family practitioners on a daily basis. Diarrhea also contributes to the nearly 450,000 admissions that occur each year for gastroenteritis (1.5% of all adult hospital admissions). Clinicians need to be able to quickly process historical clues to identify potential underlying etiologies in order to streamline the evaluation in a cost effective manner and administer appropriate treatment. From a military standpoint, diarrhea and dysenteric illnesses remain a major cause of DNBI (disease non-battle injury).

This section will provide you with a number of clinical reasoning tools to assist you with the approach to diarrhea. This includes: 1) key findings (i.e. differential diagnosis for bloody vs. nonbloody diarrhea, systemic vs. no systemic symptoms), 2) schemas (acute vs. chronic diarrhea), 3) heuristics (i.e. when to consider moderate to severe illness and staged approach to diagnosis and treatment).

Framework for categorizing diarrhea. In order to correctly diagnose and manage a patient with diarrhea, one must be able to structure the approach in a focused manner. One of the most basic distinctions is sorting diarrhea into either acute or chronic illness. Acute diarrhea may be defined as an increased number of stools that are looser in consistency than normally experienced by the patient, often accompanied by abdominal cramping, bloating or gas and rarely extending beyond 3 weeks. Older definitions that included stool weight have largely been abandoned.

Acute diarrhea tends to be mild and self-limited, though it can be severe – as in the case of dysentery - and require hospitalization for treatment. Most acute diarrhea stems from the exposure to an infectious agent or ingestion of an offending medication. Once the exposure is no longer present, the diarrhea will often resolve on its own.

Chronic diarrhea is defined as the presence of persistent multiple loose stools for greater than 4 weeks, and there are a myriad of causes that need to be explored in order to arrive at the correct diagnosis. Although many sophisticated laboratory, microbiologic, and endoscopic tools exist to assist the physician, the most effective, and least expensive, tool remains the history and physical examination.

After separating a patient into the acute or chronic category, it is most useful to subdivide acute diarrhea based on its clinical presentation. This not only helps focus one’s thought processes along certain groups of disorders, but helps in the triage process as well. The sorting process involves assessing for four clinical aspects of the presentation. Is the diarrhea bloody or non-bloody? Are there systemic symptoms or no systemic symptoms? (Table I)

ACUTE DIARRHEA

Acute bloody diarrhea with systemic symptoms.

Systemic symptoms include fever, chills, rigors, abdominal pain, tenesmus, rashes, myalgias, and arthralgias. Possible etiologies includes acute flares of inflammatory bowel disease (IBD), with
acute ulcerative colitis presenting like this more commonly than Crohn's colitis; ischemic colitis and infectious diarrhea caused by enteroinvasive pathogens to include *Shigella, Salmonella, Campylobacter, Enteroinvasive E.coli* (EIEC), *Enterohemorrhagic E.coli* (EHEC) 0157:H7 and *Entameba histolytica*. While diarrhea is a nuisance disorder for most, this group of patients represents those that may be significantly ill and require emergent attention.

Historical questions to ask these patients include any prior history or family history of IBD, any history of cardiac problems (atrial fibrillation, dilated cardiomyopathy) that could cause systemic embolic disease, or any history of atherosclerotic peripheral vascular disease (looking for evidence to support the possibility of intestinal ischemia). Remember to inquire about recent travel and eating at picnics, banquets, or from street vendors. Because of the potential severity of 0157:H7 EHEC, ask if there was any exposure to potentially contaminated foods like meat and poultry that may not have been properly cooked. Ask about other contacts including trips to farms or petting zoos, swimming, and recent treatment with antibiotics.

### Acute bloody diarrhea without systemic symptoms.

This group includes the initial presentation of colon cancer, bleeding diverticula, vascular ectasias, radiation proctitis, idiopathic ulcerative proctitis, or inadvertent over-anticoagulation with coumadin. Historically, radiation proctitis and coumadin use should be easy to determine by reviewing the past medical history. Ulcerative proctitis can be quickly assessed with a flexible sigmoidoscopy examination whereas colon cancer identification may require a full colonoscopy. Diverticular bleeding usually presents with more dramatic bleeding and the culprit diverticulum is rarely identified endoscopically.

### Clinical Scenario: EHEC diarrhea:
A 21 yo Army E4 comes to your clinic complaining of 2 days of crampy abdominal pain, watery diarrhea (>10 stools in 24 hours) progressing quickly to bloody diarrhea with worsening pain. She eats most meals at restaurants or take out including lunch from the same Chinese food stand every afternoon where she ordered steamed rice with beef. She is afebrile and her vitals are stable, but she is ill-appearing. Heart exam reveals regular rhythm but tachycardic, lungs are clear to auscultation. Abdomen is tender on palpation, no rebound, no guarding, there are hyperactive bowel sounds. There is good rectal tone, maroon stool, no perianal masses or fistulas. She is admitted to the hospital, labs including stool cultures are obtained. She is given intravenous fluid resuscitation and started on IV antibiotics. On hospital day 2, stool cultures return and are positive for *E.coli O157H7*. Antibiotics are stopped, IV fluids are continued, and anti-diarrheals are avoided while she is kept inpatient for observation and by hospital day 3 she is feeling better. The case is reported to local board of health. discharged home

### Acute non-bloody diarrhea with systemic symptoms.

Clinical Scenario: Painless hematochezia: A 74 yo retired Navy RADM with past medical history significant for diabetes and hypertension. He reports being treated with antibiotics 2 years ago for diverticulitis. He has had 1 day of red or maroon stools with intermittent passage of clot. Initially, there was stool mixed with blood, but now it is nearly completely liquid blood with clot. He denies abdominal pain, fever, chills, nausea, or vomiting. He reports feeling light headed with moving from sitting to standing. On exam he is afebrile, and at rest he is not tachycardic. His blood pressure is 140/79. With sitting up, his heart rate increases by 15 BPM while blood pressure is nearly the same. He is admitted to the hospital and given intravenous fluid resuscitation. His bloody bowel movements continue overnight, and he requires two units of packed red blood cells. Colonoscopy the next day reveals red blood throughout the colon. There are numerous large and small diverticuli in the sigmoid and ascending colon but no active bleeding is identified.
This is by far the most common group mainly because it includes most of the enteric infectious diarrheas (excluding the enteroinvasive organisms). Because of this large infectious group, one needs to pursue a rigorous history looking for possible sources of infection to include any recent travel. Questions should focus on consumption of uncooked or undercooked food, raw fruits or vegetables, seafood, meats, non-bottled water, and purchase of food from street vendors. Remember that even in a 4-star restaurant, there is still the dishwasher who is often the lowest paid, least educated (and therefore perhaps least sanitary) employee. Inquire about any new pets or illnesses in household contacts especially children. If there are children in the family, you need to determine if they attend day care centers where potential acquisition of infectious pathogens can occur. Children in day care centers have been repeatedly shown to be sources of Shigella, G.lamblia, Rotavirus and Campylobacter infections. Inquire about occupations looking for potential exposure as a health care provider. Chronic care facilities, like nursing homes, can be sources for intestinal infections in employees. Also, try to see if there is any correlation between the onset of the diarrheal symptoms and the patient’s dietary history for the preceding 24 hours. If there is an acute onset of profuse vomiting with abdominal pain followed by diarrhea within 8 hours of eating, one should consider potential ingestion of a pre-formed toxin in the food from pathogens such as Staphylococcus aureus or Bacillus cereus. Question if the patient attended any large gatherings where potential food spoilage could have occurred and if anyone else was taken ill. Finally, remember to ask if any antibiotic has been used over the preceding several months looking for potential antibiotic-associated colitis caused by Clostridium difficile.

Acute non-bloody diarrhea without systemic symptoms.

This category includes irritable bowel patients (who usually present with chronic diarrhea), lactose intolerance, medication-induced diarrhea, laxative abuse, excessive consumption of dietetic products, and inadvertent ingestion of environmental toxins. Review the medication profile of these patients looking for the addition of new medications, any new use of OTC medications or supplements, excessive use of liquid or elixir-type medications (these often contain sorbitol), or any recent change in a medication's dosing. Look for a possible connection between diarrheal symptoms and the consumption of lactose products, the initiation of new diets or excessive use of dietetic products. An occupational history may help uncover exposure to toxins such as pesticides.

Diagnostic evaluation of Acute Diarrhea.

A diagnostic evaluation is recommended for patients that show signs or symptoms of moderate or severe illness. These include:

Clinical Scenario: Pre-formed enterotoxin mediated diarrhea: You are stationed at EMF Kuwait. A 31 yo Marine E6 who has an unremarkable past medical history comes to your clinic complaining of loose stools, without blood, up to 10 bowel movements in the last 24 hours. He also complains of crampy abdominal pain bilaterally below the umbilicus. He complains of nausea with some bilious vomiting near the start of his symptoms but none in the last 24 hours. He denies fevers, or drenching sweats but notes some subjective chills without rigors, and states he feels dizzy. The symptoms began 36 hours ago. He denies any sick contacts but states 2 days ago he was at a BBQ for his friends who are returning to CONUS next week. On physical exam he is afebrile, not tachycardic with normal blood pressure. His mucus membranes are moist, and capillary refill is normal. You prescribe oral re-hydration solution, send stool sample for culture, fecal leukocytes and have him come back to the clinic the next day. He reports that he is feeling better, the pain having nearly resolved. His bowel movement frequency has decreased, and his stools now are partially formed.

Acute non-bloody diarrhea without systemic symptoms.

This category includes irritable bowel patients (who usually present with chronic diarrhea), lactose intolerance, medication-induced diarrhea, laxative abuse, excessive consumption of dietetic products, and inadvertent ingestion of environmental toxins. Review the medication profile of these patients looking for the addition of new medications, any new use of OTC medications or supplements, excessive use of liquid or elixir-type medications (these often contain sorbitol), or any recent change in a medication's dosing. Look for a possible connection between diarrheal symptoms and the consumption of lactose products, the initiation of new diets or excessive use of dietetic products. An occupational history may help uncover exposure to toxins such as pesticides.

Diagnostic evaluation of Acute Diarrhea.

A diagnostic evaluation is recommended for patients that show signs or symptoms of moderate or severe illness. These include:
- severe abdominal pain
- temperature >101.3 F
- signs of hypovolemia
- bloody diarrhea
- passage of >6 stools per 24hr with duration of illness lasting >48 hrs
- elderly (>70) or immunocompromised patients and
- recent use of antibiotics.

Most patients who have a self-limited illness with no evidence of dysentery can be observed and given supportive care (i.e. oral rehydration). If there are any historical clues of recent seafood ingestion, travel, camping, antibiotic use, homosexual activity or clinical signs of fever, abdominal pain, tenesmus, marked dehydration, then the algorithm would recommend evaluation of the stools for the presence of blood, mucus, pus or fecal polymorphonuclear cells (PMNs).

A positive response to the above could lead to a sigmoidoscopic examination together with stool cultures for enteric pathogens and C. difficile toxin if indicated. Recall that the use of a stool specimen for O&P has little utility for the patient that develops diarrhea after 3 days in the hospital. The sigmoidoscopy would allow for observation and biopsy of the distal colonic mucosa. If the patient is HIV positive, one would need to expand the cultures to include Treponema pallidum, N. gonorrhoea, C. trachomatis, CMV, HSV, and MAI. The differential diagnosis here would also include enteroinvasive pathogens, ulcerative proctitis, radiation proctitis, or IBD. If no abnormalities were found, and there continues to be bloody diarrhea, a colonoscopy would be indicated to rule out colon cancer, vascular ectasias, possible diverticular bleeding and right-sided Crohn's colitis.

Alternatively, if there is no blood, mucus, or pus, the next step would be evaluation for fecal ova & parasites on three separate stool specimens looking mainly for Giardia and E. histolytica plus Cryptosporidium, Microsporidium and Cyclospora in HIV-infected patients.

If the stool evaluation at this point remains negative, the physician is still faced with a broad differential diagnosis to include noninvasive infectious agents that are not identified in routine stool cultures, food poisoning, lactose intolerance, medication-induced diarrhea, laxative abuse, and hyperdefecation from thyrotoxicosis. At this point, the physician needs to selectively pursue other tests as indicated by the patient’s history and some of the additional classification schema may be useful at this point. Think broadly as you may be seeing the initial presentation of what may end up falling into the chronic diarrhea category.

Table 9-2 from Slesinger and Fordtran 8th edition, chapter 9 provides a nice table of causes of diarrhea in well-defined patient groups.

**Treatment Options in Acute Diarrhea.**

The cornerstone of diarrheal therapy regardless of its etiology is the replacement of the extracellular fluid deficit caused by the diarrhea. Assessment of a patient's fluid status can be quickly made at the bedside by assessing the moistness of their mucus membranes, their skin turgor, the presence of tachycardia, orthostatic hypotension and looking for evidence of a toxic appearance with fluctuation in the patient's mental status. After the fluid status is determined, the options include oral vs. intravenous (IV) rehydration either alone or in combination with antimotility agents +/- antibiotics.
There are many commercially available oral rehydration formulas designed for specific target populations (i.e. Pedialyte for infants, Gatorade/Powerade for adults or the inexpensive oral rehydration formula developed by the World Health Organization). These formulas rehydrate patients based on the principal of carbohydrate (glucose) absorption by small bowel intestinal epithelial using a cyclic AMP independent transport system. Glucose absorption is combined with simultaneous reabsorption of sodium and water from the bowel lumen into the intravascular compartment. This physiologic mechanism works even in cases of toxin stimulated fluid secretion seen with V. cholera and enterotoxigenic E. coli (ETEC). The only contraindications to oral rehydration therapy include altered mental status, the presence of an ileus, or persistent vomiting. However, in the United States, a patient presenting with diarrhea and dehydration would most likely be given IV rehydration over oral rehydration therapy even at a marked increase in expense. The only advantages of IV hydration are being able to add HCO₃ supplementation to replace ongoing HCO₃ loss in the stools, decreasing the time needed for rehydration and its use in patients with contraindications to oral rehydration. No matter what rehydration method is used, one needs to replace the baseline fluid deficit plus ongoing diarrheal fluid losses and basal metabolic losses.

In addition to rehydration, one could use antimotility agents like Loperamide (Imodium), Diphenoxylate (Lomotil), codeine, or paregoric. These agents have been shown to lessen the duration of loose stools and increase the overall subjective feeling of wellness. However, there is concern that these agents will delay the natural peristaltic clearance of pathogens and/or their toxins thereby prolonging the illness. Since this theoretically could be a problem with enteroinvasive pathogens, a general practice guideline is to limit their use to 48 hours. If diarrheal symptoms persist, then their use should be discontinued. Remember that Lomotil contains atropine and this may be contraindicated in the elderly with glaucoma and/or urinary retention.

If one suspects an infectious cause for the diarrhea, the use of antibiotics can be considered. Enteric pathogens that have clinically documented studies demonstrating the efficacious use of antibiotics include Shigella, V. cholera, E. histolytica, Giardia, and Isospora belli. It is generally agreed that these pathogens should be treated (Table II). Other pathogens with less clear clinical studies that their eradication will decrease the course of the diarrheal illness include EPEC, EHEC, nontyphoidal Salmonella, Campylobacter jejuni, and Yersinia. In these patients, a clinical judgment as to the use of antibiotics needs to be made by the physician based on the patient’s clinical status superimposed on any underlying comorbid illnesses.

The 2001 IDSA (Infectious Diseases Society of America) practice guidelines suggested empiric antibiotics for the following groups:

1. moderate to severe traveler’s diarrhea (>4 unformed stools a day with fever, blood, pus or mucus in the stool)
2. those with >8 stools/d
3. volume depletion,
4. symptoms more than 1 week
5. those in whom hospitalization is considered
6. the immunocompromised host

The empiric therapy suggested was an oral quinolone (ciprofloxacin 500 BID, norfloxacin 400 BID, or levofloxacin 500 daily) for 3-5 days in the absence of suspected EHEC or quinolone-resistance campylobacter infection. If quinolone resistance is suspected, azithromycin 500mg/d for 3d and
erythromycin 500mg BID for 5d are alternate agents. Rifaximin is a new poorly absorbed oral agent which has also shown great efficacy in both the prophylaxis and treatment of traveler’s diarrhea.29

The use of antimotility agents should be reserved for those with no fever (low grade at most) and non-bloody diarrhea. Be aware that these agents as well as exposure to antibiotics could facilitate the development of the hemolytic-uremic syndrome in those infected with EHEC.

Finally, caution patients that secondary lactose intolerance can develop in the wake of an infectious enteritis with symptoms of lactose intolerance persisting for weeks to months before the enzyme system is reestablished in a healthy brush border.

**CHRONIC DIARRHEA**

Chronic diarrhea is defined as at least 4 weeks of multiple loose stools per day (<3). These patients are harder to assess - especially those with a longer duration of diarrhea. However, if one utilizes a structured framework to categorize patients into smaller groups, the evaluation and diagnosis will be easier. For this discussion, the patients will be classified into one of three categories based on the appearance of the stool; watery, inflammatory (mucus, pus or blood) or fatty. Once the description of the stool is known, a careful history should bring one closer to the pathophysiologic mechanism and ultimate etiology for the diarrhea.

**Watery diarrhea**

This category accounts for a majority of the clinical syndromes that you are likely to encounter and includes osmotic and secretory mechanisms. Osmotically mediated diarrhea is suspected when diarrhea is present after an ingestion and is absent when fasting. To understand osmotically driven diarrhea it is important to understand that neither the small bowel nor colon can maintain an osmotic gradient. Therefore, when a poorly absorbed ion (Mg, PO4, SO4) or sugar (sorbitol, lactulose) is ingested, it obligates the bowel to maintain an intraluminal osmolality equal to that of body fluids. With body fluids having an osmolality of about 290 mOsm/kg, approximately 3.5 mL of water (1000 mL/kg divided by 290 mOsm/kg) are retained for every 1 mOsm of retained ions or molecules.

Secretory diarrhea has numerous causes but always boils down to a mechanism that is rooted in either net secretion of excess anions (bicarbonate or chloride) or net inhibition of the absorption of sodium. The most common cause of secretory diarrhea is infection (think of cholera as the ultimate secretory diarrhea). Another large category responsible for secretory diarrhea is the endocrinopathies (hyperthyroidism, Addison’s disease) and neuroendocrine tumors (VIPoma, gastrinoma, carcinoid, somatostatinoma, medullary cancer of the thyroid) whose peptide/hormone products result in secretion.

When looking for a potential secretory diarrhea, question the patient in regard to their recent travel, both locally and out of the country, looking for exposure to non-purified water and potentially contaminated food items. Try to determine if there is a correlation between the diarrheal symptoms and any recent trips. Diarrhea induced by the secretory effect of bile acids is seen with resections of < 100 cm terminal ileum or secondary to the deconjugation of bile acids in bacterial overgrowth syndromes. An additional mechanism of bile acid induced diarrhea is seen with bile acid deficiency secondary to bile acid malabsorption after ileal resections of > 100cm. These patients have steatorrhea which is an osmotic diarrhea not secretory.
Watery diarrhea may also stem from post-surgical states (post-vagotomy, post-sympathectomy) and other conditions that result in altered motility that speeds luminal fluid past absorptive sites in the intestine (e.g. diabetic autonomic neuropathy, diarrhea-predominant IBS)

**Inflammatory diarrhea**

Chronic inflammatory diarrheas are characterized by diarrhea that contains mucus or pus (fecal leukocytes). Stool with this appearance results from invasion, disruption or ulceration of the mucosa as occurs with infection, idiopathic inflammatory bowel disease or neoplastic processes that disrupt the mucosa. As such, the best diagnostic strategy for these patients includes serologic tests or culture for the appropriate pathogens (C. difficile, cytomegalovirus, Entamoeba histolytica, Yersinia spp, and Mycobacterium tuberculosis) and endoscopy to evaluate for neoplasia, IBD, radiation damage and ischemia.

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**Clinical Scenario: Ulcerative Colitis:** You are stationed with the 10th CSH in Baghdad. A 26 yo Army E4 with the Pennsylvania NG is referred to you for evaluation. He has been complaining of 4 weeks of worsening diarrhea now 6-8 stools per day, accompanied by red blood and sometimes with mucus. He reports rectal urgency and tenesmus. He also complains that most night he is awoken from sleep for a bowel movement. He reports that at home has been treated for “colitis” in the past. His younger sister also has been treated for colitis. He is an active smoker who recently quit since coming on deployment because he felt the available cigarettes were making his allergic rhinitis worse. On exam he is afebrile and his heart rate, blood pressure, and respiratory rate are normal. He is somewhat pale. Abdominal exam shows mild tenderness to palpation in left lower quadrant but no guarding, rebound, or tenderness. Lab review shows mild microcytic anemia. You are concerned that he has IBD and is currently flaring so he is evacuated to Germany where flexible sigmoidoscopy is done and biopsy confirms your suspicion of ulcerative colitis.

**Fatty diarrhea**

Chronic fatty diarrhea is known as steatorrhea and is most often associated with the chronic exocrine insufficiency stemming from chronic pancreatitis or from the lack of bile in the lumen to permit adequate fat digestion. The clinical description of fatty diarrhea is stool with aporridge-like consistency that is very difficult to flush, may cling to the sides of the toilet bowl, and may have fat droplets that are seen in the toilet water. Sudan stain for fecal fat and 24hr fecal fat collection (on the appropriate diet) are required to make this diagnosis with more certainty. A level of 14g fat/24hr collection or greater has the greatest specificity for fat malabsorption. For a valid study, patients should consume 70 to 100 g of fat per day for a few days before and during the timed collection. Be aware that measurement of fecal fat can be compromised by ingestion of the lipase inhibitor orlistat or by the fat substitute olestra.

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**Clinical Scenario: Steatorrhea:** A 68 yo woman comes to your office complaining of diarrhea with 3-5 loose, semi-formed stools that have a foul odor, are sometime foamy or greasy and typically float at the top of the bowl. She has history of alcohol abuse, and complications of alcohol use including alcoholic pancreatitis. You review prior abdominal films and notice some calcifications in the pancreatic bed and a sentinel loop of bowel. You send a stool sample for sudan stain, and it returns positive.

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**Organic vs. Functional Diarrhea.**
It is often clinically useful to triage patients based on the suspicion of an organic versus functional cause. In fact, one of the reasons that the group of patients with chronic diarrhea are more difficult to assess than those with acute diarrhea is the large percentage of functional patients. Historical aspects that suggest functional diarrhea include absence of any weight loss, having only a daytime stooling pattern, lack of blood or PMNs in the stool, and a long history of bowel problems dating back to adolescence. On the other hand, the presence of > 5 kg of weight loss, the presence of nocturnal bowel movements and a relative short duration of diarrhea (<12 weeks) suggests an organic illness. On laboratory evaluation, a high erythrocyte sedimentation rate (ESR), a low serum hemoglobin, and hypoalbuminemia also suggests an organic illness (Table III).

Clinical Scenario: Functional diarrhea. A 38 year old Air Force MAJ who works at the Pentagon comes to your clinic complaining of 5 years of diarrhea. On closer questioning she has alterations in her stool habits often with 1-2 week periods of constipation and associated bloating and pain followed by 4-5 days of loose to watery stools up to 7 times a day. These diarrheal stools are sometimes accompanied by a film or mucous, but never with blood. Her abdominal pain and bloating are temporarily relieved by the bowel movement but always return. The alterations in her bowel movements are often accompanied by stress at home or work. Your review of the chart reveals that she has gained 5 pounds in the last 3 years, is not anemic, has normal liver and kidney function and has had multiple x-rays and CT scans by other providers for similar complaints which are negative. You discuss with her your diagnosis of IBS and re-assure her that she does not require further work up, and you would like to begin symptomatic treatment.

Diagnostic Evaluation of Chronic Diarrhea in Immunocompetent Hosts.

After reviewing the patient's history, a focused approach based on clinical clues should be undertaken. The approach suggested by Donowitz et al. in a 1995 NEJM article is still pertinent today and proposes a 3-stage approach to these patients. A modification of their approach is as follows:

In Stage 1, patients should submit stools for enteric pathogens, ova & parasites, C. difficile, 72-hour fecal fat specimen, and a separate sample for stool Na⁺ and K⁺ and stool osmolality to determine the stool osmotic gap. Stool osmotic gap = 290 - 2(stool Na⁺ + K⁺ concentrations), and if the gap is greater than 50 mOsmols one can suspect an unidentified osmotically active agent. Simple screening blood tests should be obtained to include CBC, ESR, TSH, serum electrolytes, BUN, and creatinine. A sigmoidoscopy looking for melanosis coli and multiple biopsies even if the mucosa is endoscopically normal should be done to exclude collagenous or microscopic colitis. Radiographically, you could obtain a plain abdominal film looking for calcification of the pancreatic bed seen in chronic pancreatitis and barium studies to include UGI series, enteroclysis, and an air contrast barium enema. If lactase deficiency is suspected, a breath H₂ test would be indicated.

If this evaluation is negative, then most of the items on Table III would be eliminated. What would not be excluded includes laxative abuse, irritable bowel syndrome, and rare hormone producing tumors. Therefore in Stage 2, stool and urine samples should be sent for alkalinization or alternatively for thin-layer chromatography or spectrophotometry to detect the presence of the laxatives; phenolphthalein, bisacodyl, or anthraquinones. Stool should also be analyzed for Giardia antigen which has a high sensitivity and specificity.

Finally in Stage 3, one could perform an upper endoscopy or small bowel enteroscopy together with colonoscopy with terminal ileal intubation would complete the workup. During these
endoscopic procedures, biopsies should be taken to assess for IBD, infiltrative diseases such as scleroderma, amyloid or lymphoma, and chronic relapsing colonic infections of amebiasis. Upper tract biopsies would help with celiac sprue, *Giardia*, and a duodenal aspirate for quantitative bacterial cultures to exclude small bowel overgrowth.

**Diarrhea in Immunocompromised Hosts (Table V).**

A population that requires special consideration is the immunocompromised, specifically the HIV population. With the use of HAART therapy, etiologies beyond infection need to be considered in this group. In addition, medications taken and recent changes in medications, status of HIV disease (CD4 count, viral load) and co-morbid illnesses can influence the presentation and search for a pathogen.

After looking at medications, the initial step in the HIV population is trying to determine whether there are small bowel, colonic or anorectal symptoms as certain pathogens have a predilection for particular regions. Small bowel symptoms are typically watery, large volume diarrhea associated with bloating, gas, cramping and weight loss. Large bowel (colonic) symptoms are typically more frequent, small volume, often painful stools. Since the colon is a storage/water conservation organ, nutritional compromise should not be seen with an illness that is confined to the colon. Anorectal pathogens are suspected in those that practice anoreceptive sexual habits and are manifest by severe tenesmus, dyschezia, and fecal urgency.

Some pathogens which may be present in both immunocompetent and immunocompromised patients will not lead to symptoms until severe immune compromise is present – hence the importance of checking a recent CD4 count.

The first step in an HIV infected patient is an assessment for stool ova and parasites (3 specimens should be checked to increase the yield). Stool should be checked for culture, *C. diff*, and acid-fast smear to look for cryptosporidium, isospora and cyclospora. Microsporidia are usually not suspected until the CD4 count is <100 cell/microl and a trichrome stain is needed to detect their presence.

The morphologic feature used to identify the specific pathogen is the diameter for the oocyst found in stool. Microsporidium's oocysts are small measuring 1 to 2 um, Cryptosporidium are intermediate in size at 5 um while *Cyclospora* are large at 8 to 9 um. Diagnosis truly is dependent upon having a well-trained and interested parasitologist in the hospital laboratory.

The role of upper endoscopy is most useful for those with advanced immunocompromise and fever or persistent severe diarrhea with wasting or weight loss/nutritional compromise. Small bowel biopsies should be taken to assess for MAC, lymphoma, and microsporidiosis. Kaposi’s sarcoma could also be diagnosed by endoscopy. Colonoscopy may be helpful to assess for right-sided CMV if sigmoidoscopy (the more cost-effective examination) is negative, yet suspicion remains high.

Unlike CMV, HSV is a more localized infection confined to the distal sigmoid colon/rectum and esophagus. Clinically it manifests less often as diarrhea and more frequently as a proctitis with associated rectal pain, tenesmus, and mucopurulent discharge. When the infection extends into the sigmoid, then diarrhea is a more common occurrence. Tissue can be sent for virus isolation and histologically examined for intranuclear inclusions in multinucleated cells from affected areas.
Finally, remember that zinc-deficiency, which is common in HIV-infected patients may also present with a pathogen-negative chronic diarrhea. While zinc-supplementation seems to help children with zinc-deficiency related diarrhea, its use has not been shown to benefit adults with HIV related zinc-deficiency diarrhea. 30

**Answers to original clinical scenarios.**

As you have read, there are numerous causes for diarrhea. The first step is to categorize the diarrhea as acute or chronic. The first case is an example of chronic diarrhea. This diarrhea can be further categorized into inflammatory or fatty or watery chronic diarrhea. This patient has chronic watery diarrhea. The underlying causes of watery diarrhea are either secretory or malabsobtion. Your differential now should include post infectious lactose deficiency, ingestion of sorbitol or other mannitol derivatives, giardiasis, schistosomiasis, other parasitic infections, hyperthyroidism, Addison’s disease, VIPoma, and post infectious IBS.

The historical clues of recent travel in the third world should indicate to you that this is likely to be travel-related, and thus related to either chronic infection or some lingering effects of and enteric infection. All the etiologies associated with this history would be malabsorptive. In starting your evaluation you might follow the recommendations above and check a stool osmolality, stool culture and stool ova and parasite ID exam, as well as consider a giardia Ag. In this case you would find a gap of >50 which suggest an active osmole.

This would quickly reduce your differential to malabsorptive diarrhea and you then would review the clinical history being sure to eliminate any ingestions and then might send your patient for hydrogen breath testing or empirically try a lactose free diet. Either approach would lead to the correct diagnosis of post infectious lactase deficiency.

The second case is an example of acute diarrhea. The blood in stool would support an inflammatory cause. The differential diagnosis would include ischemic colitis, inflammatory bowel disease, (specifically ulcerative colitis) and infectious colitis secondary to organisms such as E coli, Shigella, or Yersinia. A flexible sigmoidoscopy was performed and revealed an area of mucosal inflammation in the sigmoid colon characterized by ulcerations, erythema, and edema consistent with ischemic colitis. On history, she has two risk factors for the development of ischemic colitis. The first is a history of a systemic vasculopathic disorder (SLE), and the other is oral contraceptives. Interestingly, she also takes a triptan for migraines, which has also been associated with ischemic bowel disease. The location of the disease is classic as it typically affects the watershed region of the colon.

**Practice Questions:**

1: Which of the following organisms may cause bloody diarrhea?

a. Enterotoxigenic E. coli
b. Norwalk virus  
c. Vibrio cholera  
d. Entamoeba histolytica  
e. Salmonella  

2: A 25 year-old woman has abdominal pain and diarrhea for many years. Her examination and basic labs are unremarkable. Her symptoms are classic for IBS and she wants to know what this diagnosis means. You tell her which of the following?

a. Her risk of colon cancer is increased  
b. It will progress to the point of colon surgery  
c. It will lead to weight loss and gut failure  
d. It may never go away  
e. It will increase her risk of complicated pregnancies.
Pediatric Addendum: Diarrhea in Children

Your next patient has a chief complaint of diarrhea. Upon reviewing the chart, you learn that he is an overall healthy 30 month old child and has not been seen since his last well-child visit at 24 months of life. Upon entering the room, you notice a very active, happy child. His grandmother is with him today because his single, active duty mother has been deployed for the past 4 months. She reports that he has 4-5 watery stools per day that leak out the diaper. This has been going on for about 3-4 weeks. There are some days that are better than others, in that he only stools 1-2 times per day, but it is always loose and large volume. He has been interested in potty training, but his grandmother is reluctant to take off the diapers due to his diarrhea. His diet seems age-appropriate, with a good mixture of meats, vegetables, and fruits. His grandmother limits his sugary treats. She recently stopped giving him milk because she was concerned that he had lactose intolerance, as it runs in the family. She wants to know if she can give him imodium to slow down the frequency of the stools. Since he refuses to drink water, she gives him juice several times a day. He has not had any fevers and she has never seen any blood in his stool. He never seems to be in pain. He stays at home with her during the day and does not attend daycare. He has never had diarrhea in the middle of the night. He has not had any recent travel.

Diarrhea in children, as in adults, is categorized into acute and chronic diarrhea. By definition, diarrhea that lasts for more than 2 weeks (unlike 4 weeks in adults) is considered chronic in a pediatric patient. The most common cause of acute diarrhea is acute gastroenteritis, caused by an infectious agent, most commonly a virus. Rotavirus and noroviruses are the most common viral agents in the United States transmitted via the fecal-oral route. There is currently an effective live-attenuate vaccine against Rotavirus. Food-borne outbreaks of diarrhea in the U.S. are most commonly due to Salmonella and Campylobacter. Unlike adults, most cases of antibiotic-associated diarrhea in children is caused by a medication side effect and not by C. difficile. The most common complication of acute diarrhea is dehydration which can be life-threatening in small children. Generally, children with gastroenteritis also have associated abdominal cramps and vomiting as well. Stool cultures should be obtained in cases of bloody diarrhea to evaluate for a bacterial cause of gastroenteritis that could be treated with antibiotics.

Chronic diarrhea in children has a broad differential diagnosis and the first step, as in adults, is to determine if the cause is osmotic or secretory. As in adults, osmotic diarrhea tends to be less voluminous, stops with fasting, has a low Na+ content, is positive for reducing substances, and has a lower pH. The opposite parameters are true for secretory diarrhea. Osmotic diarrhea is caused by the presence of a non-absorbable solute in the GI tract. The classic example is lactose intolerance, although congenital lactase deficiency is exceedingly rare (50 cases worldwide) and adult-type lactose intolerance is due to a physiologic decline in lactase. Other rare causes include congenital malabsorption syndromes and ingestion of nonabsorbable solutes, like those found in the laxative, lactulose or Milk of Magnesia (Mg hydroxide). The most common cause of diarrhea associated with malabsorption (reducing substances and/or fecal fat found in stool) is the post-gastroenteritis malabsorption syndrome. In those cases, diarrhea persists after a bout of gastroenteritis due to a post-infectious secondary lactase deficiency. Typically, when milk is avoided for 3-5 days, the diarrhea improves.

Secretory diarrhea is classically caused by a bacterial pathogen, like E. coli. Parasitic infestations, like Giardia or cryptosporidia can also present with chronic diarrhea. Inflammatory bowel disease, celiac disease, and cow’s milk protein allergy are other common causes of chronic diarrhea in children. Before the adolescent years, irritable bowel syndrome is rarely diagnosed.
In order to determine if his diarrhea has impacted his weight, you plot his height and weight on a growth chart. He is at the 75th percentile for both and has been tracking there for the past year. You are reassured that he likely does not have an underlying chronic disease, specifically celiac disease. His physical exam and vital signs are normal. Even so, you decide to order initial stool studies to include stool pH, reducing substances, fecal leukocytes, fecal fat, ova and parasites in addition to a stool culture. You also decide to order baseline labs to include a CBC, ESR, and a basic metabolic panel to include electrolytes and renal function tests. Upon further questioning, you learn that he is drinking 5-6 'sippy' cups per day of diluted apple juice, for a total volume of about 50-60 oz per day. After quantifying the juice intake, before you present the case to your preceptor, you read about "toddler's diarrhea." This is high on your differential and you are confident that reduction in his juice intake, thereby reducing his sorbitol intake (a nonabsorbable sugar,) will improve his diarrhea. Your attending agrees with your assessment and in addition to that recommendation, you advise his grandmother not to use anti-motility agents. There is no data to suggest a clinically significant benefit and the possible side effects are serious in small children and include lethargy, ileus, and respiratory depression.

SUMMARY

Diarrhea continues to be a major cause of mortality and morbidity in third world countries as well as a major symptomatic complaint in the primary care setting in the United States. The best approach to sorting these patients is by using historical clues to attempt to categorize the patients into various subgroups. Using this approach, one can quickly categorize patients with diarrhea and undergo a streamlined evaluation. Not all patients require a diagnostic workup. A large number of patients may only require oral rehydration and careful observation over time with or without use of antimotility agents. In toxic appearing patients, however, or patients with fever, bloody stools, abdominal pain or tenesmus, a selective diagnostic workup is indicated. Antimicrobial therapy is not always required. Some pathogens clearly call for treatment while some have less clear indications and other pathogens are not responsive to antimicrobial agents at all. Finally, one needs to remember that the differential diagnosis of both acute and chronic diarrhea includes many noninfectious origins.
Table I: Acute Diarrhea by Clinical Presentation

**Acute bloody diarrhea with systemic symptoms**
- Inflammatory bowel disease - Ulcerative colitis flare > Crohn's disease
- Intestinal ischemic - Arterial or venous thrombosis, arterial emboli, non-occlusive mesenteric ischemia and bowel strangulation
- Amebiasis or strongyloides
- Enteroinvasive pathogens - *Shigella, Salmonella*, Enteroinvasive *E.coli*, Enterohemorrhagic *E.coli* (0157:H7), *Campylobacter* or +/- *Yersinia*

**Acute bloody diarrhea without systemic symptoms**
- Colon Cancer
- Ulcerative proctitis
- Radiation proctitis
- Diverticular bleeding
- Vascular ectasias
- Anticoagulant medication

**Acute non-bloody diarrhea with systemic symptoms**
- Viral gastroenteritis - Rotavirus or Norwalk
- Bacterial infections - Enterotoxigenic *E.coli*, *Vibrio cholera*, *Aeromonas*, parasitic infections - *Giardia lamblia*, *Entameba histolytica*
- Food Poisoning - Pre-formed toxins of *Staph.aureus*, *Bacillus cereus*
- Antibiotic associated colitis - *C. difficile* colitis
- Endocrine - Thyrotoxicosis
- Non-bloody presentations of IBD

**Acute non-bloody diarrhea without systemic symptoms**
- Irritable Bowel Syndrome
- Lactose intolerance
- Medication induced - quinidine, colchicine, furosemide, thiazide, theophylline, misoprostel, gold, mesalamine, antacids, anticholinesterase inhibitors
- Laxative abuse - lactulose, castor oil, milk of magnesia, magnesium citrate, senna
- Bisacodyl, phenolphthalein, polyethylene glycol purge
- Toxin ingestion - organophosphates, insecticides
- Dietetic products
### TABLE II: ANTIMICROBIAL THERAPY FOR ACUTE INFECTIOUS DIARRHEA

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antimicrobial</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Shigelloides</em></td>
<td>TMP-SMZ</td>
<td>160mg/800mg</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>500mg</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><em>Vibrio cholera</em></td>
<td>Tetracycline</td>
<td>500mg</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>300mg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Travelers'</em></td>
<td>Ciprofloxacin</td>
<td>500mg</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>TMP-SMZ</td>
<td>160mg/800mg</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>Metronidazole</td>
<td>250mg</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td><strong>Protozoan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Entamoeba</em></td>
<td>Metronidazole</td>
<td>750mg</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>Iodoquinol</td>
<td>650mg</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>250mg</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Quinacrine</td>
<td>100mg</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td><em>Isospora belli</em></td>
<td>TMP-SMZ</td>
<td>160mg/800mg</td>
<td>2</td>
<td>7 to 14</td>
</tr>
<tr>
<td><em>Cyclospora</em></td>
<td>TMP-SMZ</td>
<td>160mg/800mg</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>
### Table III: Chronic Diarrhea - Clues to distinguish Organic from Functional Illness

<table>
<thead>
<tr>
<th>Organic Illness</th>
<th>Functional Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short duration diarrhea (&lt;12 weeks)</td>
<td>Long duration  Daytime only diarrhea</td>
</tr>
<tr>
<td>Nocturnal diarrhea</td>
<td>No weight loss</td>
</tr>
<tr>
<td>Weight loss &gt; 5 kg</td>
<td>Laboratory clues</td>
</tr>
<tr>
<td>Laboratory clues</td>
<td>Anemia, hypoalbuminemia</td>
</tr>
<tr>
<td>Elevated sedimentation rate</td>
<td>Normal screening laboratories</td>
</tr>
</tbody>
</table>

### World Health Organization Oral Rehydration Solution

- 3.5gm sodium chloride
- 2.5gm sodium bicarbonate
- 1.5gm potassium chloride
- 20gm glucose or 40gm sucrose
**Table IV: Differential Diagnosis for Chronic Diarrhea In the Immunocompetent Hosts**

**Osmotic diarrheas** (unabsorbed solutes)
- Lactase deficiency
- Laxative abuse - MgSO₄, lactulose
- Dietetic supplementation - Sorbitol or mannitol additives
- Carbohydrate malabsorption 2° to celiac sprue
- Steatorrhea
- Small bowel overgrowth

**Secretory diarrheas** (altered intestinal ion absorption/secretion)
- Bile acid diarrhea
- Laxatives - Athracene products, bisacodyl docusate, ricinoleic acid
- Infections - Cholera and ETEC (usually always acute presentation)
- Hormone secreting tumors - Carcinoid, ZES, VIPoma, Medullary thyroid cancer, Large villus adenoma.
- Chronic Epidemic diarrhea (Brainerd and Henderson County epidemic)

**Inflammatory diarrheas**
- Inflammatory bowel disease
- Ischemic colitis
- Radiation colitis/enteritis
- Chronic relapsing infections, - Giardia, Amebia, C. Difficile.
- Partially obstructive colon cancers.

**Dysmotility disorders**
- Irritable bowel syndrome
- Neuropathies - Diabetic or Alcohol induced
- Hyperthyroidism
- Previous surgery - vagotomy, gastrectomy, cholecystectomy, and Intestinal resections.

**Infiltrative diarrheas**
- Microscopic colitis
- Lymphomas
- Amyloid
- Lymphocytic colitis
- Scleroderma
### Table V: Differential Diagnosis of Chronic Diarrhea in the Immunocompromised Host

<table>
<thead>
<tr>
<th>Protozoal Infections</th>
<th>Fungal Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Microsporidium</td>
<td>Coccidiomycosis</td>
</tr>
<tr>
<td>Isospora belli</td>
<td>Candida albicans</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td></td>
</tr>
<tr>
<td>Cyclospora</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td></td>
</tr>
<tr>
<td>Leishmania donovani</td>
<td></td>
</tr>
<tr>
<td>Blastocystis hominiae</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral Infections</th>
<th>Bacterial Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>Mycobacterium avium complex</td>
</tr>
<tr>
<td>HSV</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Shigella</td>
</tr>
<tr>
<td>Rotaviruses</td>
<td>Salmonella</td>
</tr>
<tr>
<td>Norwalk</td>
<td>Campylobacter</td>
</tr>
<tr>
<td>HIV</td>
<td>C. difficile</td>
</tr>
<tr>
<td></td>
<td>Vibrio species</td>
</tr>
</tbody>
</table>


14.) Ungar BL, Yolken RH, Nash TE, et al: Enzyme-linked immunosorbent assay for the

28) Clinical Infectious Diseases 2001; 32:331


Introduction to Clinical Reasoning

ACUTE AND CHRONIC DIARRHEA

CASE 1

**HPI:** Your patient, a 42 y.o. woman whom you have not seen in the past year comes to the clinic complaining of abdominal discomfort and diarrhea of four months duration. She was late for her appointment because she had to volunteer at her daughters’ Montessori school (pre-K) for the morning. The patient states that she has been under a great deal of stress for the past 3 years with the birth of her twins (4th and 5th children) and is having a hard time “keeping it all together”. Her first 3 children range in age from 13 to 17. Among her litany of complaints, the patient states that she has been sleeping poorly, eating hurriedly, and unable to get to the gym anymore. She previously played tennis and swam at least 4 days a week. Her general health has remained good during this time but the abdominal discomfort and diarrheal frequency has become a real problem for her, and she felt it was “time to check it checked out”. You recall that she has a family history of colon cancer (her father died from colon cancer at age 52) and note that you had meant to get her in for her first screening colonoscopy at age 40.

Historically, her stool frequency has been somewhat erratic, sometimes going 3 to 4 times a day alternating with episodes where 4 to 5 days may pass without a bowel movement along with gas, cramps and bloating. Now, however, she complains of peri-umbilical to right lower quadrant cramping associated with loose, poorly-formed, unformed stools up to 5 times a day. She feels as if she is not eliminating completely yet has been self-medicating with an over-the-counter remedy for constipation that she bought while attending her mother’s funeral 6 months ago. She does not recall its name. With her poor sleep she has been waking up at nights but can’t seem to relate these awakenings to the need to have a bowel movement. Upon review of the medical record you see that she has been in to see a mental health provider for anxiety and depression that began shortly after her mother’s death, and she has been taking an SSRI.

**Past Medical History:** The patient has a long history of fibromyalgia and feels that her symptoms are beginning to worsen since she is no longer exercising regularly. She had been taking low dose amitriptyline for her symptoms as well but this was stopped when she was started on her SSRI. She has well controlled hypertension on HCTZ. She was recently seen in the walk in clinic for a sinus infection and had a course of Augmentin (amoxicillin and clavulanate) for this.

**Physical Examination:** Blood pressure is 145/74, pulse is 88 and regular, respirations are 18, temperature 99.6, weight is 130 pounds, height is 67”. Patient is a well-developed female in no distress during the examination. HEENT exam is unremarkable but you think the thyroid may feel a bit large. Heart and lungs are normal. Abdominal exam reveals tenderness periumbilically to palpation. There is no organomegaly noted, and bowel sounds are active. Rectal exam is unremarkable with no stool in the vault.
DISCUSSION QUESTIONS FOR CASE 1

1.)  What is the differential diagnosis of this patient's complaint?

2.)  What additional history would be helpful?

3.)  List your diagnostic approach to this patient in order of decreasing importance?

4.)  What is the possible significance of the antibiotic therapy?

5.)  Is the description of nocturnal events helpful?

6.)  How does the family history impact your thought process with this patient?

7.)  Do you need to do anything for this patient today?
ACUTE AND CHRONIC DIARRHEA CASE 2

**HPI:** During Spring break, your friends are planning a trip to Mexico and you want to go along but are a poor, cash-strapped medical student. You cash in your air miles in order to fly there and are lucky enough to crash on the floor of one of your friend’s hotel rooms for lodging. Fortunately for you, while your friends are “wasting money” at the expensive chain restaurants on the strip, you find that not only are you getting to experience authentic Mexican cuisine, you are saving lots of money on the very tasty, yet inexpensive food in the family-run restaurants that the taxi driver who brought you from the airport to the hotel recommends to you. You have also been able to save money by filling up during the day on all the fresh fruit from the fruit bowl in your friend’s hotel room. Your behavior has been a bit out of control with too much Tequila at night but at least you have remembered to hydrate yourself by drinking lots of water during the day. Unfortunately, after 3 days of paradise you awaken on the 4th day to incredible waves of abdominal cramps that are soon followed by voluminous, foul-smelling, watery diarrhea. You realize that you can’t afford to go see a local physician in Cancun and so you check with your friends to see whether anyone brought any medications with them. Even more fortunate for you, your friends have a lot more common sense than you and insist on checking you over themselves before allowing you to be your own physician.

**Physical Examination:** Your blood pressure is 112/60, heart rate is 95, temperature is 100.5°F. Skin turgor is normal. Abdominal exam revealed tenderness to deep epigastric palpation. There was no evidence of organomegaly. Bowel sounds were hyperactive with audible borborygmi. You are close friends, but rectal examination is deferred nonetheless – who takes guaiac cards on vacation anyway?

**DISCUSSION QUESTIONS FOR CASE 2**

1. What is your differential diagnosis?

2. List several risk factors that could have led to diarrhea in this patient?

3. Is there anything else that could have been done to avoid developing diarrhea?

4. Should this patient be treated with an anti-diarrheal agent?

5. Does this patient need antibiotics? Explain the pros and cons of antibiotics
CASE 3

You are attending the wedding of your old college fraternity brother and are catching up on things with mutual friends at the reception when your friend’s mother comes to you – the doctor - soliciting help for a “crisis” that has developed. It seems that over the past 2 days, several of the guests have come to the groom’s mother asking whether she had some Imodium they could use. At first, the mother just thought that her guests were not used to the foods that were being served, but now she has become more concerned with the presentation of the 5th and 6th ‘patients’. Your roommate is from Puerto Rico and you have flown there with several of your old fraternity brothers and their families to attend the wedding. You all have busy schedules and needed a break and therefore have been in Puerto Rico for the past week to combine the wedding with some vacation time. You feel a bit nervous to be put on the spot like this but are confident that your lectures on diarrhea from medical school have prepared you well for this situation. When you ask the groom’s mother about the details she is concerned that the guests may have become ill from something specific they may have eaten, and she wants to make sure no one else gets sick.

The afflicted individuals range in age from 2 to 57 and include the infant daughter (2) of one of your frat brothers who normally spends her days in daycare while her parents work in the family-owned and operated pet store, one of the groom’s aunts (57 years old) an avid outdoorswoman that came directly to the wedding from Colorado after a 2 week hike in the Rockies, a cousin (23) that has just returned from a year in the Peace Corps in Malaysia, an uncle (47) who is attending the wedding with his same-sex “roommate” whom he has lived with for the past 15 years, and finally the bride and her mother. The bride is a thin anxious 26 year old woman who has had a “nervous stomach” all of her life, the mother is a 53 year old woman who has had prior “ulcer surgery” for refractory ulcer disease as a teenager.

None of the patients appear gravely ill but a few look sick enough to get your attention and a few are concerned about what to do about their diarrhea – especially since some will be traveling home soon and are concerned about whether they will be able to tolerate the travel.
DISCUSSION QUESTIONS FOR CASE 3

1. List the most likely causes for each patient:
   a. the 2 year old infant
      
      i. does the family business affect the situation?
   
   b. the 57 year old outdoorswoman
      
      i. what if she had been hiking in Nepal instead?
   
   c. the 23 year old Peace Corps worker
      
      i. is there anything particular about the area of the world she worked in?
   
   d. the 47 year old uncle
   
   e. the 26 year old bride
   
   f. the bride’s mother
      
      i. how does the surgical history affect the situation
         
      ii. what if the surgery resected a tumor rather than part of the stomach? What kind of tumor may it have been?
CASE 4

HPI: A functional 76 yo grandmother, visiting her children for the summer in upper state New York, was brought to the local ER with severe diarrhea over the last 48 hours. She reported upwards to 15 to 20 loose, watery, non-bloody stools each day. The patient complained of associated abdominal cramps with nausea and multiple episodes of bilious vomit. Her family felt she was not thinking as clear as her usual baseline, she was not taking anything by mouth and she had not urinated that day. Two days prior to the onset of symptoms, her family had a family reunion/picnic. The main food was hot dogs, hamburgers, barbecued chicken and potato salad. The patient avoided these products except for a single baloney sandwich. Because of the summer heat she drank freshly prepared lemonade and apple juice. There was no well water on the farm.

She normally lives in Boston, and this is the only trip in the last 12 months except for a 1 week vacation to Bermuda this Spring. Shortly after returning from that trip she did develop travelers' diarrhea that was successfully treated with Pepto-Bismol and Septra. That illness was nowhere near as severe as her current diarrhea. She has no pets but her children own an apple orchard which has multiple farm animals to include horses, cows and pigs that grazed in the orchard.

Past Medical History: She has ASCAD S/P non Q wave MI 10 years ago, hyperlipidemia, hypertension, and a H/O atrial fibrillation in the past that is chemically controlled with quinidine and on ASA prophylaxis. Her only other medication is lisinopril for hypertension.

Physical Examination: In the ER, her vital signs were HR of 110 and regular, temperature of 99.6°F, respirations 20. Her BP supine was 148/60 and sitting on the stretcher was 118/48. She felt too dizzy to stand up to complete the tilts. She was WD, WN but appeared lethargic. Her HEENT exam revealed dry buccal mucosa, sunken eyes and her skin tented. Her chest and lung examination were WNL except for tachycardia. Her abdomen had mild tenderness to palpation in all 4 quadrants without rebound or masses. Her rectal exam was without masses, the stool was light green and FOBT positive. Her labs revealed a normal Hgb of 14.2, normal platelets of 242,000 but a mild leukocytosis of 14,100 with a left shift.

Hospital course: She was admitted for rehydration. After 24 hours on the ward, her stool studies came back as negative ova and parasites, negative C. difficile toxin, negative enteric pathogens to include Shigella, Salmonella and Campylobacter. However, her diarrhea became progressively bloodier with increasing abdominal pain. A CT scan of her abdomen showed thickened loops of colon and an air contrast barium enema showed thumb-printing. A repeat CBC showed a drop in both her Hgb to 10.2 and her platelets to 86,000. The peripheral smear showed evidence of a hemolytic anemia. Her renal function reveals acute renal failure with a creatinine of 4.2.
DISCUSSION QUESTION FOR CASE 4

1.) What is the differential diagnosis for bloody diarrhea?

2.) What risk factors does she have for bloody diarrhea?

3.) During her hospital course, what syndrome did she develop?

4.) If this is ischemic colitis, what are her risk factors? How do you make the diagnosis?

5.) Given the stool culture results, could this still be due to an infectious agent? If so what agent and how would you make the diagnosis?

6.) What is this patient’s prognosis?
INTRO TO CLINICAL REASONING: JAUNDICE

Objectives:

1) Understand the production and excretion of bilirubin. This understanding needs to be used in conjunction with a careful history and physical examination and the appropriate selection of diagnostic studies to identify the cause of jaundice. This includes how to rule out non-hepatic causes of jaundice (clue = indirect bilirubinemia)

2) Know the indications and limitations of the diagnostic studies available to evaluate a patient with an elevated bilirubin.

3) Classify abnormal liver tests as HEPATOCELLULAR versus CHOLESTATIC injury

4) List the laboratory tests that can be used to identify common, specific causes of hepatocellular (i.e. ceruloplasmin, hepatitis serologies, alpha-1 antitrypsin) and cholestatic (i.e. antimitochondrial antibodies) disease entities

5) Understand the interpretation of viral hepatitis serologies

Key Definitions:

Jaundice - A yellowish discoloration caused by accumulation of bile pigments.

Cholestasis - Inhibition of bile flow.

Cholangiogram - Imaging of the biliary system. Can be obtained endoscopically, percutaneously, intraoperatively, and by MRI.

Cirrhosis - Widely distributed hepatic fibrosis in which fibrous strands encircle hepatocytes to form nodules. The fibrosis and disrupted hepatic anatomy prevents
normal blood flow through the liver and results in **portal hypertension.** Hepatic fibrosis is caused by liver parenchymal cell death and chronic inflammation.

**Patient A:**

A 28 year old male patient has been referred for the evaluation of jaundice. He is a medical student studying for his USMLE Step 2 Exam. He states that his girlfriend noticed mild yellowing of his eyes 3 days ago, and that his skin began yellowing approximately 24hrs later. Aside from being fatigued from non-stop studying, he is feeling generally well. He has no prior medical history and takes no medications except ibuprofen or Tylenol for the occasional headache. He has no surgical history and his family history is unremarkable. He consumes 3-4 alcoholic beverages over a weekend 1-2 times each month, but denies any other recreational drug use and is a life-long non-smoker. His physical exam is entirely normal except for scleral icterus and mild diffuse jaundice. Labs are notable for a total bilirubin of 4.0 mg/dL (direct bilirubin is 0.2 mg/dL), with a normal alkaline phosphatase, aminotransferases, and electrolytes. BUN and creatinine are 18 and 1.1 respectively.

1. What additional labs would be helpful at this time?
2. Based on the above information, what imaging study/studies is/are warranted?
3. What would be in your differential diagnosis?
4. What if the CBC revealed a normocytic anemia?
5. What if the patient were recently started on rifampin for a furuncle on his thigh?
6. What if the patient had undergone a laparoscopic appendectomy 5 days earlier?

**Patient B**

A 32 year old active duty sailor presents to sick call on his destroyer with jaundice and dark urine. He had been seen several days earlier in sick call with a complaint of nausea and vomiting as well as malaise and vague abdominal pain. Symptoms were attributed at that time to viral gastroenteritis and he had been treated with supportive care only before being sent back his quarters for 3 days of SIQ. These symptoms resolved soon thereafter, but since then he has noticed progressive yellowing of his skin. He is otherwise feeling well, though he admits to diffuse mild itching. He denies any further abdominal pain and is having no fevers, chills or night sweats. He has no significant past medical history, has had no surgeries and takes only a protein supplement purchased at the GNC store on base. He has no significant family history. He drinks socially on weekends, getting drunk 3 or 4 times each month, but has no daily alcohol consumption. He denies any other recreational drug use and he is a lifelong non-smoker. He works as a sonar tech and has no known occupational exposures. His ship is currently on cruise in the South Pacific with stops in Thailand and the Philippines within the past 6 weeks. On exam he is afebrile and normotensive. He has scleral icterus and diffuse jaundice. Remainder of the exam is within normal limits except for mildly tender liver, palpable 4 cm below the costal margin. Labs are notable for a total bilirubin of 10 mg/dL (direct bilirubin 8.0 mg/dL), alkaline phosphatase 250 U/L, AST 600 U/L,
ALT 900 U/L and albumin of 3.6 g/dL. His WBCs are 11.2 x10^3/uL, and he has a normal Hgb and platelets. His INR is 1.1. The remainder of his labs, including electrolytes, BUN and creatinine are within normal limits.

1. Describe this patient’s pattern of liver test abnormalities
2. Based on the above scenario, what would be in your differential diagnosis?
3. What other laboratory tests are warranted at this time?
4. What imaging studies are warranted?
5. A viral hepatitis panel is ordered. It reveals positive HAV Ab, and HBsAb, with negative HBsAg, HBCAb, HBeAg, HBeAb and HCV Ab. How do you interpret these results and are there any other tests you might want to order to clarify the diagnosis?
6. If this patient had recently been injured and was taking oral pain medicines, what additional etiologies would need to be considered?
7. What should be suspected if his initial AST were 200 U/L and ALT 100 U/L?
8. What if this was a 65 year old male smoker with being treated for lung cancer?

**Patient C**

A 68 year old female retired Army nurse presents to the emergency room for evaluation of jaundice which began 2 days ago. She complains of moderate fatigue which has been ongoing for 2 months, but denies any fevers, chills, nausea, vomiting or abdominal pain. She does admit to tea-colored urine and pale gray (clay colored) stools over the past 2 days. She has mild hypertension which she treats with diet modification only and as no other significant past medical history. She denies any prior history of jaundice, takes no medications and is a lifelong non-smoker. She denies any significant alcohol use. On physical examination, she is afebrile and normotensive. She has scleral icterus and diffuse jaundice. Her examination is otherwise notable for a non-tender abdomen with no Murphy’s sign, but with a palpable gallbladder and no stigmata of portal hypertension.

Laboratory evaluation includes a total bilirubin of 10 mg/dL (direct bilirubin 8.0 mg/dL), alkaline phosphatase 250 U/L, AST 90 U/L, ALT 95 U/L and albumin of 2.7 g/dL. Her WBCs are 8.0 x10^3/uL, and she has a normal Hgb and platelets. Her INR is 1.0. The remainder of her labs, including electrolytes, BUN and creatinine are within normal limits.

1. How would you characterize this patient’s pattern of liver enzyme abnormalities?
2. What further labs or imaging studies are warranted at this point?
3. What are the most likely causes of this patient’s jaundice?
4. How would this change if this patient were febrile and having right upper quadrant abdominal pain?
5. What additional diagnosis should be considered if this patient had a history of Ulcerative Colitis?
6. What if this patient were 36 year old on HAART therapy for HIV?
Jaundice and Hepatic Injury

I. Physiology of Bilirubin Metabolism

A. Production: Bilirubin is the final product of the degradation of heme. Most of the heme (75-80%) comes from hemoglobin following the breakdown of senescent red blood cells. The remainder of heme is produced by degradation of heme containing enzyme systems (primarily the cytochrome p450 system in the liver). The enzyme heme oxygenase degrades heme to biliverdin. Biliverdin is then reduced by biliverdin reductase, to bilirubin. Degradation of the RBCs and production of bilirubin occurs in the reticuloendothelial system. Normally, about 300 mg is produced daily.

B. Transport and Uptake: (from the RE system to the hepatocyte)

1. Bilirubin (unconjugated at this point) is water insoluble and attaches to albumin for transport in the circulatory system. The unconjugated fraction of bilirubin equivalent to indirect reacting bilirubin.

2. Albumin delivers bilirubin to sinusoidal surface of the hepatocyte. A carrier-mediated process uptakes bilirubin into the hepatocyte. The carrier-mediated process operates far below saturation and is not rate limiting.

C. Cytosol Transport and conjugation: (in the hepatocyte)

1. Bilirubin (unconjugated at this point) is transported in the cytosol to the endoplasmic reticulum (ER) by Ligandin which is also known as glutathione S-transferase or Y protein.

2. Conjugation: Conjugation occurs in the ER by the microsomal enzyme, uridine diphosphate glucuronosyltransferase (UDP-GT). One or two glucuronide molecules will be conjugated to the bilirubin molecule (monoglucuronide 30%, diglucuronide 70%). This bilirubin complex is now water soluble (direct fraction).
D. **Excretion**: The conjugated bilirubin is then excreted into the bile canaliculus by a poorly understood mechanism. Starting at the canaliculus, bile flows from intrahepatic → extrahepatic biliary system and is then excreted into the small intestine.

E. **Intestinal Conversions**: A small amount of bilirubin will undergo conversion in the small intestine by bacteria to urobilinoids (primarily urobilinogen). The urobilinogen will then be reabsorbed into the circulation and undergo uptake and excretion by the liver. Urobilinogen is water soluble and can be filtered in the urine. Large amounts of urinary urobilinogen can be seen in liver dysfunction and in overproduction states.

**Summary**: bilirubin metabolism is the body's process of taking a toxic water insoluble substance (bilirubin) and making it water soluble (to facilitate excretion from the body). The process of making bilirubin water soluble is the conjugation of bilirubin to the glucuronide molecule which occurs in the hepatocyte.

II. **Clinical Classification of Jaundice**:

A. **Excess in production**. (usually only causes mild elevation of bilirubin)
   - hemolysis and hematoma.

B. **Defective** bilirubin clearance by the liver hepatocyte (hepatocellular defect).
   - hepatocellular injury from viral hepatitis.

C. **Decreased** bilirubin excretion (obstructive/cholestatic defect)
   1. **Intrahepatic** - Obstruction occurs at the level of the canaliculus or within the small hepatic biliary ducts.
      - Primary biliary cirrhosis (PBC), drug induced liver injury (DILI), sepsis, certain infections
   2. **Extrahepatic** - Obstruction occurs in the large bile ducts, common bile duct, or at the ampullary apparatus. Used to be known as "surgical jaundice" until the advent of alternative endoscopic and radiographic treatment options for biliary obstruction.
      - Common bile duct stone, ampullary carcinoma.
III.  **Historical Features in the Evaluation of Jaundice**

A. **Demographics:** Infectious causes (viral hepatitis) are more likely in younger patients, and malignancy is more common in older patients. Primary biliary cirrhosis and autoimmune chronic active hepatitis are conditions more common in females while primary sclerosing cholangitis is a condition that is more common in males. Viral hepatitis is more common among Asian- and African-born individuals.

B. **Abdominal pain:** The following types of pain may be seen in patients with jaundice. These are general classifications and it is important to understand abdominal pain presentations may vary widely between patients.

1. **Biliary Colic** - An episodic severe pain usually located in the epigastrium/right upper quadrant. Pain typically has a sudden onset over 15 minutes, plateaus for 3-6 hours and then slowly resolves. This visceral pain is thought to originate from tonic spasm resulting from transient obstruction of the cystic duct by a stone.

2. **Hepatic capsule** - Occurs in hepatocellular disease such as viral and alcoholic hepatitis. The liver swells and places tension on the liver capsule. It is perceived as a dull achy right upper quadrant pain.

3. **Parietal peritoneal pain** - Peritoneal irritation may occur secondary to adhesions from the hepatic capsule to the parietal peritoneum or from direct irritation of the peritoneal cavity from infection or malignancy.

4. **Pancreatic** - An unrelenting pain to the back. May be associated with a pancreatic cancer or chronic pancreatitis.

C. **Prodromal Symptoms.**

1. Anorexia, malaise, nausea, low grade fever, and arthritis which occur 1-2 weeks before the onset of jaundice suggest viral hepatitis.

2. Weight loss and constant epigastric pain suggests neoplasm.

D. **Pruritus:** Suggestive of an obstructive/cholestatic process.

1. Incidence of pruritus:

   - Primary Biliary Cirrhosis: 99%
   - Malignant obstruction: 75%
   - Benign obstruction: 50%
   - Hepatitis: 20%
Cirrhosis 10%

E. **Color of Urine and Stool:** Dark urine (Coca-cola or tea colored) may antecede clinical icterus by one to several days. Acholic (light or clay colored) stools occur due to loss of urobilinoids.

F. **Race:** There is an increased incidence of hemolysis due to G6PD deficiency in individuals with African and Mediterranean ancestry.

G. **Occupation:** History for exposure to hepatic toxins (e.g. vinyl chloride) and infectious agents (e.g. medical personnel, endemic areas) should be assessed.

H. **Drug History:** Prescription, OTC and alternative/herbal drugs can cause hepatotoxicity, hemolysis, and increase the incidence of gallstones and pancreatitis. Pay particular attention to supplements in the Active Duty population.

I. **Social History:** Alcohol consumption, illicit drug use, sexual habits should be assessed (multiple partners, anal intercourse, intranasal cocaine).

J. **Exposures:** Historical data such as needle punctures (illicit and accidental), transfusions, travel, and association with patients with hepatitis/jaundice should be assessed.

K. **Family History:** Review for history of liver disease (e.g. hemochromatosis, Alpha-1 antitrypsin deficiency, hepatitis B), jaundice (Gilbert's syndrome, Dubin-Johnson syndrome, Rotor's syndrome) and hemolysis (hereditary spherocytosis).

L. **Past Medical History:** Important information includes history of cholelithiasis, biliary surgery, malignancies, congestive heart failure (causes passive liver congestion), inflammatory bowel disease (associated with primary sclerosing cholangitis), pancreatic disorders, and blood donations (letters are sent if screening hepatobiliary enzymes are abnormal or if viral markers are positive). If the patient has a history of a cholecystectomy then it is important to determine if the patient did indeed have gallstones and if an intra-operative cholangiogram was performed at the time of surgery.

IV. **Physical exam:**

A. **General:** Evaluate nutritional status (body habitus and evidence of peripheral muscular
wasting), mental status (hepatic encephalopathy), presence of icterus, and for physical exam evidence of chronic liver disease.

1. Bilirubin binds to elastin. Areas of the body which are high in elastin (sclera, tissue under the tongue) will show evidence of jaundice the earliest.
   a. Scleral icterus = Usually can be detected at 2.5 - 3.0 MG/DL range
   b. Upper body discoloration more pronounced than the lower body at levels less than 15 MG/DL
   c. Usually not noticed by the patient first, but by a friend or relative
   d. Lag period exists between the darkening of the urine and noticeable jaundice

B. HEENT: Kayser-Fleischer rings secondary to copper deposition in the lens of the eye are seen in Wilson's disease. Palpable xanthomas (subcutaneous fat deposit)- biliary cirrhosis. Fetor Hepaticus - hepatic encephalopathy. Parotid gland enlargement is associated with cirrhosis and alcohol.

C. Chest: Gynecomastia (chronic liver disease P.E. finding).

D. Abdomen: Surface inspection - Caput Medusa is a prominent superficial vein pattern that radiates from the umbilicus and indicates portal hypertension. Liver - Assess size, contour, tenderness, and consistency. Spleen - Splenomegaly may indicate portal hypertension. The spleen is palpable in 50% of patients with cirrhosis. Gallbladder - Distended palpable gallbladder classically associated with malignant obstruction distal to the cystic duct insertion (Courvoisier's sign), but may occur in up to 25% of patient with common bile duct stone obstruction. Ascites - May be difficult to distinguish from fat, flatus, feces, fetus, and tumor.

E. Skin: Evaluate for vascular spiders. These small telangiectasia are commonly found in patients with cirrhosis and located above the nipple line. "Spiders" can also be found in normal children, pregnant women and those taking oral contraceptives. Bronze skin pigmentation is seen in patients with hemochromatosis (Bronze Diabetes). Excoriations are commonly associated with
pruritus. Easy bruising is associated with coagulopathy and thrombocytopenia. *Palmar erythema* (liver palms) is associated with chronic liver disease.

F. **Extremities:** *Dupuytren's contraction* (painless thickening and contracture of tissue beneath the skin on the palm of the hand and fingers → PE finding in cirrhosis, alcohol, men>women).

G. **Genitalia:** Testicular atrophy and hypogonadism (primary gonadal injury & suppression of pituitary/hypothalamic function)

H. **Neurologic exam:** Asterixis and cogwheel rigidity is seen in hepatic encephalopathy. A timed standardized "connect the numbers trail test" can be used to assess the progression or improvement in patient with encephalopathy.

V. **Differential Diagnosis of Jaundice**

**A. Bilirubin Overload** (primarily unconjugated)

1. **Hemolysis**

   a. **Red blood cell defects**

      (1) *Congenital:* Hereditary spherocytosis, glucose 6-phosphate dehydrogenase deficiency (G6PD), sickle cell disease, thalassemia
      (2) *Acquired:* Vitamin B12 and folic acid deficiencies, paroxysmal nocturnal hemoglobinuria

   b. **Extra-erythrocytic factors:** Isoantibodies, chemicals, infection, venoms, transfusion reaction, alcohol, paroxysmal hemoglobinuria.

   **Comment:** In the absence of liver disease, patients with severe hemolysis rarely have a 17:9
serum bilirubin level greater than 4-5 MG/DL.

2. **Non-hemolytic types**
   a. *Gilbert's syndrome* (heads up, 8% of your class may have this) -
      - Autosomal dominant
      - Defect is decreased activity of UDP-GT
      - Results in increased unconjugated bilirubin
      - Total bilirubin mildly elevated (rarely goes > 4.5 MG/DL)
      - Normal liver aminotransferases and histology
   b. *Crigler-Najjar syndrome* (types I and II)
      - Type I Virtual absence of UDP-GT (fatal)
      - Type II Decreased level of UDP-GT
   c. *Dubin-Johnson syndrome*
      - Defect is the excretion of conjugated bilirubin from the hepatocyte
   d. Congestive heart failure

**B. Hepatocellular Disease**

1. Acute hepatocellular dysfunction
   a. Infection: viral, bacterial, protozoal
   b. Alcohol
   c. Drug induced
   d. Ischemia
   e. Associated with other diseases: carcinoma, Hodgkin's disease, abscess, sepsis
   f. Total parenteral nutrition (TPN) – can be cholestatic as well
   g. Autoimmune
   h. Wilson disease
   i. Acute fatty liver of pregnancy

2. Chronic hepatocellular dysfunction
   a. Any of the above injuries can become chronic. The most common disorders leading to
chronic liver disease are viral (hepatitis B and C), alcohol, autoimmune, and drug.

b. Hemochromatosis
c. Alpha-l-antitrypsin deficiency

**C. Biliary Obstruction**

1. Intrahepatic Obstruction/Cholestasis
   a. Biliary atresia
   b. Primary sclerosing cholangitis (PSC)
   c. Primary biliary Cirrhosis
   d. Metastatic carcinoma
   e. Lymphoma
   f. Caroli's disease - (Congenital dilation of intrahepatic/extrahepatic bile ducts)
   g. Intrahepatic bile duct carcinoma
   h. Granulomatous
   i. Benign cholestasis of pregnancy

2. Extrahepatic Obstruction/Cholestasis
   a. Choledocholithiasis (stones in the common bile duct)
   b. Bile duct strictures (benign and malignant)
   c. Carcinoma of the head of the pancreas
   d. Cholangiocarcinoma
   e. Carcinoma of the papilla of Vater
   f. Primary sclerosing cholangitis
   g. Biliary atresia
   h. Choledochal cysts
   I. Metastatic tumors invading the CBD or in the porta hepatitis compressing the CBD.
   J. Parasitic infections (flukes, ascariasis)
   k. Suppurative cholangitis
   l. Hemobilia (Blood originating in the biliary system)
Comment: Several of these disorders are on the intra and extrahepatic categories. Many of these disorders can involve both areas. Two cholestatic disorders are of special interest and will be further expanded below.

Primary Sclerosing Cholangitis (PSC)
- Inflammatory thickening and segmental fibrosis of the larger bile ducts.
- Immune system mediated
- Occurs primarily in young males under the age of 45
- 75% of patients also have ulcerative colitis
- 5% of patients with ulcerative colitis will have PSC
- High risk for cholangiocarcinoma

Primary Biliary Cirrhosis (PBC)
- Autoimmune disorder of the very small bile ducts. These ducts are slowly damaged → disappear → cirrhosis
- Predominately seen in middle aged females
- Elevated alkaline phosphatase (often found spuriously)
- Positive anti-mitochondrial antibody (AMA) in 95% of cases

VII. Tests and Procedures to Evaluate the Hepatobiliary System
Comment: A single test to measure liver function is not available. Thus liver function can be estimated from a number of tests. The laboratory studies described below are classified as tests that detect cellular injury, tests that measure hepatic transport and synthetic function, and tests that assess chronic inflammation and immunoregulation. Purists will admonish you for using the term "liver function tests" when reporting aminotransferase or alkaline phosphatase values. These studies do not measure liver "function" and are only markers of hepatocyte damage (“liver associated enzymes”).
A. Laboratory (test to detect injury to hepatocytes)

1. Serum aminotransferases (transaminases)
   AST - Aspartate aminotransferase (SGOT)
   ALT - Alanine aminotransferase (SGPT)
   a. ALT is more sensitive and specific for liver cell injury
   b. AST is also found in cardiac m., skeletal m., kidney, brain, pancreas, lung, and leukocytes
   c. Elevation represents generalized damage to the hepatocytes
   d. Poor correlation between level of elevation and extent or severity of liver disease
   e. If levels are greater than 1000, suspect viral, toxic or ischemic injury
   f. AST/ALT ratio:
      - If >1 and ALT is < 100 = suggests alcoholic liver disease
      - If >2 = strongly suggests alcoholic liver disease
   * Pyridoxal 5'-phosphate is necessary for the activity of both aminotransferases, but ALT has enhanced sensitivity of alcohol induced pyridoxine deficiency. Thus in alcoholic liver disease, the AST is greater than the ALT.

2. Alkaline Phosphatase
   a. Family of enzymes that catalyze the hydrolysis of organic phosphate esters
   b. Found on exterior surface of bile canalicular membrane
   c. Also found in bone, kidney, intestine, WBCs, and placenta (can fractionate)
   d. Significant increase (fourfold or greater) is typically observed in patients with cholestatic processes
   e. Major mechanism underlying elevation is increased synthesis via mRNA translation of hepatic Alk Phos rather than impaired biliary

17:13
secretion.

3. Other Enzyme Markers of Cholestasis
   a. Gamma-glutamyl transferase (GGT)
   b. 5'- nucleotidase

B. Laboratory (tests of liver's capacity to transport organic anions and metabolize drugs)
1. Bilirubin (discussed previously)
   a. *Unconjugated* - Water insoluble (indirect), bound to albumin in the serum
   b. *Conjugated* - Water soluble (direct), under normal circumstances, should not be in serum. Will be filtered by the kidney when present in serum.
   c. *Delta bilirubin* - Portion of conjugated bilirubin that becomes irreversibly covalently bound to albumin and will not be cleared from the serum until albumin is degraded.
   d. Bilirubin will rise 1-2 MG/DL/day with total bile duct obstruction.
   e. Bilirubin will rarely rise greater than 30-35 MG/DL unless renal dysfunction is present.
   f. Differential of tea colored urine is bilirubinuria, myoglobinuria, and hemoglobinuria
   g. In isolated indirect hybilirubinemia, a hemolysis work up (LDH, haptoglobin, coombs test) should be performed

* It is important to note that a typical complete metabolic panel does not fractionate bilirubin.

2. Serum bile acids
   a. Synthesized in hepatocytes from cholesterol
   b. Normal levels in congenital hyperbilirubinemia disorders and hemolysis
   c. More sensitive than bilirubin for detection of liver disease but cannot quantify liver damage.
   d. Not a routine test and should not be used for screening. May be helpful in evaluating low level bilirubin elevations of unknown
cause.

e. Elevated levels in portosystemic shunting secondary to reduced hepatic extraction

C. Laboratory (tests to measure synthetic capacity)

1. Albumin
   a. Most important of the plasma proteins formed in the liver
   b. Long serum half life (20 days)
   c. Liver synthesizes 15 GM/Day, nutritional factors are very important for rate of synthesis
   d. Factors that decrease synthesis - alcohol, inflammation, TNF
   e. Factors that stimulate synthesis - TSH, corticosteroids, products of urea synthesis, amino acids (tryptophan, phenylalanine, glutamine)

2. Clotting factors
   a. 11/13 clotting factors are made in the liver
   b. Vit K dependent factors are (II, VII, IX, and X)
      Vit K is essential for the post translational formation of gamma carboxyglutamyl residues that are essential for the physiological activation of these factors
   c. Factor VII is the best index of severity for liver disease/ prognosis (short half life, 1/2 day)
   d. Prothrombin time that cannot be corrected with Vit K denotes severe liver disease and poor prognosis.
   e. Other causes of decreased Vit K - dietary deficiency, malabsorption syndromes, antibiotic use, drugs

3. Lipoproteins
   a. Lipoproteins are formed in the hepatocyte
   b. Liver forms fatty acids from carbohydrates, synthesizes triglycerides from fatty acids and glycerol, and chylomicron remnants are metabolized in the liver
   c. Abnormalities in lipoproteins and mild hypertryglyceridemia are commonly seen in hepatocellular injury
Target and spur cell formation may result from enhanced incorporation of cholesterol into the RBC plasma membrane.

4. Disease Specific Markers
   a. Ceruloplasmin
      - copper transport protein in plasma that is useful in the diagnosis of Wilson's disease (an autosomal recessively inherited copper storage disease)
      - low levels of ceruloplasmin (less than 20 MG/DL) found in 90% of patients homozygotic and 10% of heterozygotic for Wilson disease
      - typically increased in Primary Biliary Cirrhosis
   b. Ferritin
      - An iron protein complex for storage of iron
      - Elevated ferritin (usually greater than 600) with saturation of Fe/TIBC >50% is present in patients with genetic hemochromatosis
      - Estimated incidence of genetic hemochromatosis is 1/250-1/300
      - C282Y/H63D are 2 most common mutations, commercial lab test available
      - Untreated hemochromatosis can lead to cirrhosis and hepatocellular carcinoma
      - Serum ferritin is an acute phase reactant, thus hepatocellular necrosis and systemic infection can increase ferritin levels
      - Check in fasting state
   c. Alpha-1-antitrypsin (A1AT)
      - protease inhibitor synthesized in the liver - principle function is the inhibition of leukocyte elastase
      - serum levels of A1AT may increase with inflammation, malignancy, and pregnancy
      - patients with alpha-1-antitrypsin deficiency are homozygous for the electrophoretically slowest of the genetic variants of this protein (Pi ZZ), have markedly decreased serum A1AT levels and are predisposed to chronic active hepatitis and cirrhosis (incidence
- The defect in A1AT deficiency is the inability of the hepatocyte to process and secrete the Z protein. The Z protein differs from the normal M protein by a single amino acid. PAS positive diastase resistant globules of A1AT accumulate in the hepatocytes.

D. Laboratory (tests to detect chronic inflammation and altered immunoregulation)

1. Immunoglobulins
   a. Kupffer cells in the liver represent a significant part of the RE system. In cirrhosis, altered blood flow from the liver bypasses antigens normally cleared by the hepatic RE system. Systemic antigen presentation results in increased gamma globulins.
   b. IgG elevation is usually present in autoimmune chronic hepatitis
   c. IgA can be elevated in alcoholic liver disease
   d. IgM is elevated in primary biliary cirrhosis

2. Anti-smooth muscle antibody (ASMA)
   a. Reactive to S actin
   b. May be positive in up to 70% of patients with autoimmune chronic active hepatitis (ACAH)
   c. ACAH is primarily a disorder of young women

3. Anti nuclear antigen (ANA)
   a. Can be found in all types of autoimmune disease
   b. Low titers → non-specific, can be false positive

4. Anti-liver/kidney microsomal antibody (anti LKM1)
   a. Subset of autoimmune liver disease
   b. Patients are generally female and less than 25 years old
   c. Antigen to which anti-LKM1 is directed is the cytochrome

5. Antimitochondrial antibody (AMA)
   a. Four major mitochondrial antibodies related to primary biliary cirrhosis (PBC) have been described.
   b. Present in greater than 90% of patients with PBC
   c. Can also be positive in patients with autoimmune or drug induced hepatitis.
E. Laboratory (other)

1. Alpha-fetoprotein (AFP)
   a. Elevated in 60% of patients with hepatocellular carcinoma
   b. Can be elevated in patients with active hepatocellular inflammation
   c. Negative test does not exclude carcinoma
   d. Also elevated in pregnancy

2. Ammonia
   a. Toxic product of nitrogen metabolism
   b. Disposed of through the Krebs-Henseleit cycle in the liver with generation of urea
   c. Increased level in fulminant hepatic failure due to impaired conversion of ammonia to urea due to hepatocellular necrosis.
   d. Hyperammonia in patients with cirrhosis and portal hypertension reflects systemic shunting of ammonia derived from colonic bacteria

3. Platelet Count
   a. Thrombocytopenia can be indicative of hypersplenism caused by portal hypertension.

F. Radiologic Studies

1. Right upper quadrant ultrasound
   a. Evaluates liver, gallbladder, pancreas, and right kidney
   b. Most cost effective study to evaluate for gallstone disease. 90-95% sensitive in detecting the presence of cholelithiasis. Only 15-30% sensitive in identifying the presence of a common bile duct stone.
   c. Sensitive study to detect dilation of intra and extra-hepatic bile ducts
   d. Doppler ultrasonography is useful in evaluating blood flow in the hepatic, portal and pancreatic vessels.
2. Abdominal CT scan (3 phase contrast study)
   a. Provides more detailed information than ultrasound and should be first choice if
malignancy is suspected. CT scan is not as sensitive as ultrasound in detecting
gallstones.

3. MRI of the liver (with gadolinium)
   a. Valuable in evaluation of liver tumors and to assess blood flow (with Gadolinium)
   b. Noninvasive method to evaluation biliary system (MRCP)

4. Endoscopic retrograde cholangiopancreatography (ERCP)
   a. Administration of contrast into the biliary system utilizing a side viewing endoscope
   (anatomy of biliary system and pancreatic duct can be defined)
   b. Allows for therapeutic modalities (e.g. ampullary sphincterotomy, stent placement,
   stone removal, tumor brushing, and stricture dilation)

5. Percutaneous cholangiography (PTC)
   a. Alternative method to visualize biliary ductal system if ERCP is unsuccessful or
   contraindicated
   b. Transhepatic placement of a needle into the biliary system for contrast
   administration and therapeutics

6. Nuclear Medicine Studies
   a. HIDA scan
      -Technetium-99m labeled imidodiacetic acid derivative marker
      -Marker is administered IV, taken up by the hepatocyte, and excreted in the biliary system.
      -Useful in cholecystitis, cystic duct obstruction, bile duct leaks, and biliary atresia
      -A rough image of the biliary system can be obtained
   b. Liver spleen scan
      -Uptake of technetium labeled sulfur derivative by the liver RE system - Utilized in the
      past to identify space occupying lesions
      -Currently has limited value
   c. Hemangioma scan / Tagged RBC study (Technetium labeled RBC blood flow
      scan) - Utilized to evaluate for hemangiomas
7. Upper Gastrointestinal Series - Can be useful to evaluate for esophageal and gastric varices but upper endoscopy is more sensitive

G. Liver biopsy
1. Method can be percutaneous, laparoscopic, open, or transjugular
2. Allows for histologic assessment of liver tissue
3. Tissue can be assessed for quantitative iron (hemochromatosis) and quantitative copper (Wilson's disease)
4. Cultures can be obtained (FUO evaluation)
5. Contraindications to biopsy
   a. Uncooperative or unstable patient
   b. Ascites
   c. Impaired coagulation
   d. Suspected hemangioma or echinococcal cyst
   e. Right sided empyema
   f. Current use of antiplatelet agents

Viral Hepatitis and Serologic Markers
1. **Hepatitis A**
   a. Small RNA virus, enterically transmitted
   b. Incubation period 30 days
   c. Anti-HAV IgM is diagnostic of acute disease
   d. Anti-HAV IgM last for 2-6 months
   e. Anti-HAV IgG persists for life and confers long lasting immunity
   f. Does not cause chronic liver disease
   g. Vaccine available and effective
2. **Hepatitis B**
   a. DNA virus, transmitted through infected blood and body fluid.
   b. 10% of acute infections become chronic.
   c. **HBsAg** - Outer shell of this virus is called the hepatitis B surface antigen. Positive
result denotes active infection.
d. **HBeAg** - Part of inner core antigen. Persistence denotes active hepatitis replication. Must be HBsAg positive to be e antigen positive. Of note, pre core mutants are HBeAg negative.
e. **Anti-HBs** - Antibody to the surface antigen. Positive result denotes clearance of & protection from infection. Effective vaccination → positive hep B surface Ab.
f. **Anti-HBc IgM** - Antibody to the core antigen. Generally positive during acute infection and flare of hep B.
g. **Anti-HBc IgG** - Denotes prior or current infection. Vaccination cannot give a positive core antibody.
h. **Anti HBe** - Denotes clearance of the e antigen
i. **HBV DNA** - Measures presence of DNA in the serum, denotes active replication of hepatitis B if positive

Hepatitis B can cause acute disease that completely resolves (90-95%) or results in fulminant hepatic failure (less than 1%). A chronic infection can result in approximately 5% of patients. Chronic infection can lead to cirrhosis and increased risk for hepatocellular carcinoma. A patient is classified as having chronic hepatitis B if the infection persists longer than six months.

3. **Delta hepatitis (Hepatitis D)**
   a. Incomplete RNA virus that can only exist in association with hepatitis B
   b. Will present as a co-infection with hepatitis B or as a super infection in a patient with chronic hepatitis B
   c. In USA, risk factor is IV drug use
   d. Delta antigen and antibody tests are available

4. **Hepatitis C**
   a. Small RNA virus
   b. Spread by parenteral exposure, IV drug use, intranasal cocaine, and blood transfusion (rare sexual and maternal-infant transmission)
c. Hepatitis C cirrhosis accounts for highest percentage of patients on liver transplant lists
d. Diagnosis by HCV ELISA, confirmed by HCV RIBA
e. Hep C PCR denotes active infection
f. 80% of patients infected will have evidence of chronic infection
g. Antibody is detectable 3-6 months following infection
h. 4 main genotypes. 80% are genotype 1.
i. Birth cohort from 1945-65 should be screened

5. Hepatitis E
   a. Enterically transmitted small RNA virus
   b. Primarily limited to third world countries, immunosuppressed patients
   c. Clinical illness similar to hepatitis A
d. High mortality seen in pregnant females
e. Hepatitis E IgM antibody is the test of choice

Returning to our patients…..

Patient A

This young, otherwise healthy patient is experiencing mild indirect (unconjugated) hyperbilirubinemia. This occurs in the setting of any of 3 processes: increased bilirubin production, as occurs with hemolysis or reabsorption of a hematoma; impaired hepatic bilirubin uptake, which can occur if blood is being shunted from the portal circulation to the systemic circulation (portosystemic shunt), or as a side effect of certain medications (rifampin, probenecid); or impaired hepatic bilirubin conjugation, which can occur in the setting of certain hepatocellular diseases (Wilson’s, advanced cirrhosis, chronic hepatitis), in hyperthyroidism, or in inherited disorders of conjugation (Gilbert’s syndrome, Crigler-Najjar), this is also the mechanism for neonatal jaundice.

The patient in the initial scenario most likely has Gilbert’s disease. He has no evidence of hemolysis (no anemia, normal electrolytes), and has no evidence of underlying liver disease (normal liver associated enzymes), leaving impaired conjugation as the probable mechanism for his jaundice. While Crigler-Najjar is an exceedingly rare autosomal recessive disease which usually
manifests as a serious illness in infancy or early childhood, Gilbert’s disease, which results from reduced B-UGT enzyme activity, occurs in approximately 10% of Caucasians and rarely results in bilirubin levels above 4.0 mg/dL. It is a benign disease that usually manifests only in the setting of physical or emotional stress and dehydration.

No additional imaging or other labs are necessary for this diagnosis. If he did have an anemia, the work-up would have to be directed towards looking for sources of hemolysis such as syndromes of dyserythropoiesis (e.g. hereditary spherocytosis, G6PD deficiency), other intravascular hemolysis syndromes (e.g. DIC, AIHA, TTP) or extravascular hemolysis (e.g. splenic sequestration). Some medications, such as rifampin, impair hepatic uptake of bilirubin. A history of recent surgery would raise the possibility of a hematoma that is now being reabsorbed.

**Patient B**

This otherwise healthy patient with jaundice and a mostly hepatocellular pattern of enzyme elevation with very high ALT most likely has acute hepatitis A. He has a predominantly direct (conjugated) hyperbilirubinemia and his jaundice was preceded by a viral prodrome following recent traveled to an endemic area where he likely ate food prepared under uncertain sanitary conditions. His exam reveals no evidence of chronic liver disease, but he does have tender hepatomegaly. He has a high ALT with ALT>AST and with a moderately high bilirubin and alk phos and normal synthetic function. His viral labs indicate Hep A exposure and that he has been immunized against, but not infected with, Hepatitis B. He does not have evidence of Hepatitis C. A positive HAV IgM would confirm the diagnosis. Other possible etiologies to consider would be causes of chronic liver disease (e.g. Wilson’s disease, hemochromatosis, alpha-1-antitrypsin deficiency, chronic hepatitis B or C) other causes of acute hepatitis (e.g. autoimmune hepatitis, toxic exposures, alcoholic hepatitis), as well as infiltrative diseases such as sarcoidosis, tuberculosis or lymphoma. Finally hepatic vascular injuries can also cause an acute hepatocellular injury with very high ALT.

Further work-up should therefore include a ceruloplasmin, ferritin and iron panel, ANA, anti-smooth muscle antibody, and immunoglobulins. He should be screened for toxins such as cocaine and acetaminophen and should have his blood alcohol level checked. A RUQ U/S (must ask for duplex flows to rule out vascular thrombosis/Budd Chiari) or CT of the liver will be warranted if other work-up is negative.

History of recent use of pain killers should prompt concern for acetaminophen overdose, which will require immediate treatment. Lower level enzyme elevations with an AST:ALT ratio of 2:1 would suggest alcoholic hepatitis. In the patient with risk factors for hypercoagulability, or atherosclerotic disease, Budd-Chiari syndrome (IVC thrombosis) should be considered and evaluated either with Doppler study on ultrasound, or by angiography (MRA or CTA).

**Patient C**
This patient is experiencing painless jaundice with an obstructive pattern of liver test abnormalities (direct hyperbilirubinemia, elevated alkaline phosphatase with only modestly elevated aminotransferases). This pattern can be seen in any process that limits flow of bile out of the biliary tree, with limited or no hepatocellular liver injury. This can include factors that impair flow from hepatocytes into bile cannuliculi (cholestasis) or issues causing blockage of intrahepatic or extrahepatic bile ducts or of the common bile duct.

In case C, the patient’s symptoms are particularly concerning for tumor obstructing the distal common bile duct, such as a mass in the head of the pancreas, or the ampulla, inhibiting flow through the Sphincter of Oddi, or a tumor in the common bile duct itself, such as a cholangiocarcinoma. The presence of Courvoisier’s sign (a palpable non-tender gallbladder) also suggests malignant biliary obstruction, though it is neither sensitive nor specific for this. A RUQ ultrasound or an abdominal CT is usually the initial studies of choice to evaluate obstructive jaundice, in order to determine whether or not the common bile duct is dilated. If dilation is present, then further evaluation with an MRCP, ERCP or endoscopic ultrasound (EUS) is indicated, with ERCP providing the added benefit of enabling endoluminal brushings for cytology and therapeutic intervention if needed and EUS providing the opportunity for evaluation of surrounding tissues for lymphadenopathy and needle biopsy of concerning structures.

If this patient were having intermittent abdominal pain (biliary colic) then the likely source would be a gallstone obstructing the common bile duct (choledocholithiasis), which is far more common than malignancy. When jaundice and abdominal pain are accompanied by fevers, it fulfills Charcot’s triad for ascending cholangitis, which is a medical emergency requiring urgent biliary decompression. In addition to stones and tumors other possible sources of bile duct blockage include intraluminal strictures, parasites (e.g. *Ascaris lumbricoides*), or extrinsic compression from surrounding lymph nodes.

In a patient with a history of Inflammatory Bowel Disease, such as Ulcerative Colitis, a diagnosis of Primary Sclerosing Cholangitis should be considered, and imaging of the biliary tree will reveal a beaded appearance of the bile ducts, reflecting the numerous ductal strictures which form from this inflammatory condition. If no dilation of the common bile duct or of intra or extra or common bile ducts is seen on imaging, then the patient likely has intrahepatic cholestasis. This can be seen in the 3rd trimester of pregnancy, following surgery or as a result of medications. HIV medications, estrogens and anabolic steroids are among the many medications which can cause cholestasis.

**JAUNDICE: Considerations in the Pediatric population…**

*Your next patient: Upon your arrival in the nursery for morning rounds, the nurse asks you to look at an infant. She reports that the infant's skin and sclera appear yellow and that the baby is not breastfeeding well. The baby is a 3010 gram male born two days ago to a 28 year-old primigravida*
Caucasian mother. Pregnancy, labor, and delivery were uncomplicated. The infant's initial newborn exam done shortly after birth was normal. Aside from routine (once per shift) observation by the ward nurses, the infant has been rooming-in with the mother.

On your examination, you are reassured by the infant's vital signs: HR = 130/min, respirations = 40/min, T = 37.2 C, and BP 75/45. He appears well and is sleeping quietly. His skin color is a deep yellow from his head to his mid-thigh. Cardiopulmonary and abdominal examinations are normal. There is no significant bruising or other evidence of significant birth trauma. What do you think is causing this infant’s jaundice?

Jaundice is quite common in the newborn period, primarily because infants initially have relatively impaired bilirubin conjugation of from immature UDP glucuronyl transferase activity, shortened life span of red blood cells, and increased intestinal reabsorption of bilirubin. Levels of bilirubin are routinely monitored closely in the first few days to weeks of life because extreme hyperbilirubinemia in the newborn is associated with the development of kernicterus, a devastating neurologic outcome. Acutely, kernicterus manifests as poor sucking, stupor, and hypotonia. Over time, chronic kernicterus may present with dystonia and athetosis, tonic neck reflexes, tremor, upward gaze abnormalities, sensorineural hearing loss, and intellectual deficits. Conditions that disrupt the integrity of the blood brain barrier, such as sepsis, meningitis, acidosis, and prematurity, place the infant at higher risk for kernicterus.

Jaundice can be determined clinically by blanching the skin to reveal an underlying yellow color.
Jaundice begins on the face and progresses down towards the feet. The farther the jaundice progresses down the body and the more intense the color, the higher the total serum bilirubin. Most nurseries check bilirubin levels using a handheld transcutaneous device and confirm high levels with a total serum bilirubin.

Although most newborn jaundice is physiologic, the physician must always consider pathologic causes, particularly if jaundice appears within the first 24 hours of life, a rapid rise of total serum bilirubin is observed, or a total serum bilirubin level greater than 17 mg/dL in a term infant occurs. In these cases, the infant is more likely to have some underlying issue with hemolysis, infection, or occult hemorrhage such as from a cephalohematoma associated with birth trauma. Additionally, if jaundice persists beyond 2-3 weeks of life, further investigation is warranted.

Direct or conjugated hyperbilirubinemia is never physiologic and may indicate liver disease or biliary obstruction. The differential diagnosis includes neonatal hepatitis (secondary to congenital CMV, toxoplasmosis, syphilis, rubella, etc), biliary atresia, sepsis, and metabolic disorders such as galactosemia.

One of the more common causes of indirect hyperbilirubinemia is hemolysis due to ABO incompatibility, which can occur in infants who are blood type A or B and whose mothers are type O. In individuals with type A or B blood, naturally occurring anti-A and anti-B isoantibodies are primarily IgM and thus do not cross the placenta. This is contrast to individuals with type O blood whose isoantibodies are frequently IgG. If a mother with type O blood has a fetus with either type A or type B blood, her anti-A and anti-B IgG antibodies can potentially cross the placenta and cause hemolysis. Although 15-20% of mother/infant pairs are “set-ups” for this phenomenon, only
a small minority of infants develop severe hemolytic disease because anti-A or anti-B IgG antibodies may bind to non-erythrocytic cells that contain A or B antigen.

Rh blood group incompatibility is another cause of hemolysis in the newborn, but is rare today with modern medicine. An Rh-\textit{negative} mother may develop anti-Rh antibodies during “sensitization” after being exposed to Rh-\textit{positive} fetal red blood cells secondary to fetomaternal hemorrhage during pregnancy (to include abortion, trauma, obstetric procedures) or normal delivery. However, only 15-20\% of pregnant women with Rh-negative blood who are exposed to Rh-positive fetal blood cells ever develop Rh antibodies. On subsequent pregnancies, maternal Rh IgG can cross the placenta into the fetal circulation where they can bind to Rh-positive fetal red blood cells and lead to hemolysis. Therefore if the mother is a “set-up” for this phenomenon, she can be given anti-Rh-\textit{positive} immune globulin (RhoGAM) around 28 weeks’ gestation and within 72 hours of birth to prevent sensitization.

Rare causes of indirect hyperbilirubinemia due to hemolysis include red cell enzyme defects (e.g. G6PD deficiency), red cell membrane disorders (e.g. spherocytosis), and hemoglobinopathies (e.g. thalassemia).

Treatment for significant indirect hyperbilirubinemia is phototherapy, whereby special white or blue lights are positioned carefully around the infant. The lights induce photoisomerization of bilirubin, forming lumirubin, which is water soluble and excreted in the urine. If phototherapy fails and the level of indirect bilirubin is severe, then an exchange transfusion can be performed. This treatment removes partially hemolyzed and antibody-coated red blood cells and replaces them with donor cross-matched red blood cells.
Back to the patient:

You take a look at the mother’s chart and notice that her blood type is O+. You then discover that the infant’s blood type came back as A+. You perform a transcutaneous bilirubin check on the baby’s forehead several times and the level comes back around 16 each time. You want to confirm this elevated reading with a serum measurement and arrange for a venous sample to be drawn. You also decide to include a few additional stat labs. After an hour, the bilirubin comes back high at 17.5 mg/dL with a direct bilirubin of 0.2 mg/dL. At this point, you doubt it could be due to physiologic jaundice and start to consider other possible causes of indirect hyperbilirubinemia such as Group B Strep or E.coli sepsis, hemolysis from ABO incompatibility, occult hemorrhage, or G6PD deficiency. The CBC shows a WBC of 12,000 with a hemoglobin of 12 g/dL, and platelets of 313K. The reticulocyte count is 17% and an indirect Coombs test is positive. You suspect mild to moderate hemolysis from ABO incompatibility and arrange for phototherapy to be started.
ICR Jaundice Small Group Cases

Patient 1:

A 68 year old male patient has been referred for the evaluation of jaundice. He is a hospital volunteer and a fellow coworker noticed that his eyes and skin looked yellow. The patient had been feeling fatigued and anorexic for three days.

1. What additional symptoms would you want to ask about?

Past Medical history:

He denied any past surgeries. His medical problems consisted of noninsulin dependent diabetes for eight years and hypertension for five years. His medications consisted of ASA 325 mg QD, Lisinopril 10 mg QD and metformin 1000 mg BID. The metformin was initiated two weeks prior the patients illness. He was a nonsmoker. He had a history of heavy alcohol intake which he stopped 15 years ago.

2. What other historical information would you want to ask?

Physical exam: Icteric Caucasian male in no distress. BP 140/75, P 80, R 15, T 98.9

HEENT- Marked scleral icterus. Neck - no adenopathy. Chest and cardiac exams were unremarkable. Abdomen - soft with normal BS. No hepatomegaly or palpable masses.

Rectal exam showed heme negative stool. Ext. - normal. Neuro - normal. Skin- several small spider angiomata on upper trunk.

3. What additional lab studies would you want to order?

4. What radiologic studies would you want to order?

5. What is the importance of this patient's occupational exposures?

6. What is the differential diagnosis for this patient?
Patient 2:

A 24 year old female, was referred for the evaluation of upper abdominal discomfort, nausea, and jaundice. She returned to the Washington, D.C. area two weeks ago following a four week jungle training course in Panama. She was previously in good health.

1. What additional historical information may be helpful?

Past Medical History: She underwent a splenectomy at the age of nine following a sledding accident. She thinks that she did get a blood transfusion at that time. Her only medication is an oral contraceptive. GOPO, LMP two months prior. Tob - none. ETOH none but had a DUI two years ago. Family history: sister and brother are hepatitis B carriers.


Laboratory: CBC (WBC 9800 72% PMNs 3% Eos, 20% lymphs, 5% mono), normal electrolytes, AST 480, ALT 690, Alk P 198, Bili 4.2, Alb 3.9 GM/DL, Total protein 7.5 GM/DL. UA 3+ bilirubin.
2. What is the differential diagnosis for this patient?

3. What additional laboratory studies would you order?

4. What additional radiologic studies would you order?
Patient 3: (patient referred to the medical clinic from the emergency room)

A 67 year old male complains of a 6 month history of diarrhea and deep epigastric pain. The pain is constant but increases after he eats. He has lost 22 pounds during this period. His wife noticed that his eyes were yellow and forced him to come to come to the emergency room.

What other historical data would you like to ask?

Past medical history: Surgeries - Cholecystectomy at age 35. Tob - 1.5 PPD x 45 years.
ETOH - 12 pack per week. Medical - Hypertension treated for 15 years. Medications - Atenolol 50 mg QD. Allergies- none.
ROS: Significant for fatigue. Also positive for urinary hesitancy and frequency.
Physical exam: Wt 200 lb. Ht 5 ft. 11 in. BP 140/90, P 65, T 98, R 14.

17:33
Labs obtained in the ER. CBC Hct 39%, WBC 6000 (60 % PMNs, 30% lymphs, 10 % monos) 
Plt 189K. Na 145, K 3.9, BUN 12, Creat 1.3, AST 79, ALT 109, Alk Phos 309, Total protein 5.9, 
Alb 3.3, Bilirubin 8.0. UA 4+ bilirubin.

What is the differential diagnosis for this patient?

What lab studies would you order?

What radiologic studies would you order?
JAUNDICE: Considerations in the Pediatric population…

CASE: Upon your arrival in the nursery for morning rounds, the nurse asks you to look at an infant. She reports that the infant's skin and sclera appear yellow and that the baby is not breastfeeding well. The baby is a 3010 gram male born two days ago to a 28 year-old primigravida Caucasian mother. Pregnancy, labor, and delivery were uncomplicated. The infant's initial newborn exam done shortly after birth was normal. Aside from routine (once per shift) observation by the ward nurses, the infant has been rooming-in with the mother.

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INTRODUCTION TO CLINICAL REASONING:
ABDOMINAL PAIN

Fouad Moawad, MD
Patrick Young, MD

Patient 1: A 44 year-old mother of 3 presents with a 2-day history of right upper quadrant abdominal pain. She states that previously the pain typically occurred within 1-2 hours after eating food, would wax and wane in intensity, and typically resolve completely after 3-4 hours. Tylenol (acetaminophen) has not seemed to help the discomfort. It was sometimes associated with nausea and vomiting. On examination, she has a temperature of 100F, HR=90, and blood pressure of 120/70. Abdominal exam reveals decreased bowel sounds and epigastric tenderness to palpation without guarding or rebound.

Questions:
1. How would you characterize the patient’s abdominal pain?
2. What if the patient described pain that radiated to her back?
3. What additional history and/or physical examination information will help you establish the diagnosis?
4. How can laboratories and radiographs help you with the evaluation of her abdominal pain?

Patient 2: A 38 year-old woman presents with 3 days of increasing abdominal discomfort and distention accompanied by nausea and vomiting for the last few hours. She describes the pain as crampy in nature and predominantly peri-umbilical. She reports occasional abdominal pain in the past, however her pain has never been this pronounced. She has had no changes in her diet and recalls eating at a restaurant one day prior to the pain developing. On exam, she is afebrile, her pulse is 85 and her blood pressure is 120/70. Abdominal exam revealed a mildly distended abdomen with hyperactive bowel sounds and audible rushes. She also has mild tenderness to palpation throughout and tympany to percussion without guarding or rebound.

Questions:
1. What additional historical information is important in this case?
2. How can laboratory and radiographic information help with evaluation of her abdominal pain?
3. What recommendations would you give for initial management of this patient?

**Objectives:** By the end of the session, the student will be able to:

I. List *classic* history and physical exam findings associated with the following common abdominal pain syndromes:
   1. inflammatory bowel disease
   2. peptic ulcer disease
   3. pancreatitis
   4. cholecystitis
   5. appendicitis
   6. gastroenteritis
   7. acute intestinal obstruction
   8. intestinal ischemia
   9. pelvic inflammatory disease
   10. irritable bowel syndrome

II. List the classic patterns of referred pain for the above syndromes

III. List both laboratory and radiographic tests used to help “rule-in” or “rule-out” the above diagnoses

**Overview**

The abdominal pain section will illustrate the approach to abdominal pain using the key finding approach, heuristics (shortcuts), and a schema (algorithm). The sequence will follow key questions on history and physical exam as well as potentially useful laboratories and radiographs.
Furthermore, basic illness scripts (prototypic presentations) of common causes of abdominal pain are presented.

**Key Definitions and Distinctions:**

- *Acute abdominal pain* – Pain that is present for hours or days
- *Chronic abdominal pain* – Pain present for months or years
- “*Acute abdomen*” – abdominal pain with rigidity, guarding, rebound tenderness, and increased plasma leukocytes, suggesting peritoneal inflammation
Neuroanatomy, Noxious Stimuli, and Clinical Reasoning

Hollow viscera such as the stomach, small and large intestine, gallbladder, and uterus have nerve endings in their muscular wall. Solid organs such as the liver, spleen, and kidney have nerve endings in their capsules. All of these organs are relatively insensitive to stimuli such as cutting, tearing, or crushing. Instead, they are sensitive to stretching. Insult or injuries that cause stretching will cause these nerves to fire “pain” signals. Such injuries occur during rapid stretching or tension, traction, distention, forceful muscular contraction, inflammation or tissue edema, ischemia, or direct neural invasion.

How would you characterize the patient’s abdominal pain?

Types of Abdominal Pain

The patient with visceral pain – Pain from an organ

A patient with visceral pain may describe the quality of the pain as dull, cramping, burning, or gnawing. The quality of the pain also depends on the organ involved. The patient may be restless and unable to find a comfortable position. Autonomic symptoms are frequently present such as sweating, nausea, vomiting, tachypnea, and pallor.

Pain from an organ is usually perceived in the midline of the abdomen. Afferent sensory nerve fibers from the affected organ are received by both sides of the spinal cord. However, pain from the capsule of an organ lateralizes. For instance, pain from the hepatic capsule is perceived on the right side, and pain from the splenic capsule is felt on the left. The location of the abdominal pain corresponds roughly to the skin dermatome that shares the same segment of the spinal cord as the organ.

When the noxious stimulus to the viscera (i.e. ischemia or inflammation) increases in intensity, the pain may radiate from its usual midline abdominal location to a distant body site, such as the neck shoulder, or back. This phenomenon is called referred pain. It results from recruitment of additional afferent neurons from more remote body sites that share the same neurosegment of the spinal cord. Referred pain may be felt in the skin or deeper tissues and is usually fairly well localized.

The patient with colicky pain – pain from distention of a hollow viscus.

A patient with colicky pain typically describes their symptoms as “spasms” or “waves” with a waxing and waning course. Colicky pain is classically described as peaking at maximum intensity and then subsiding somewhat to a lower level, only to return to a greater severity again (crescendo-decrescendo). This pattern may continue until the pain completely subsides. There is no persistent baseline pain in a patient with colicky pain.
This is the typical description of the pain felt by patients that are passing gallstones into the common bile ducts (choledocholithiasis) with resultant spasm from the distention of the smooth muscle-lined duct or from the passage of kidney stones. Patients with partial small bowel obstruction may also experience this type of discomfort.

The patient with *parietal pain* – Pain from the *peritoneum*

A patient with peritoneal pain will describe the quality of the pain as intense, sharp, and *precisely localized*. It is often aggravated by coughing, respiration, and sudden jolts. *As opposed to patients with visceral pain, the patient with parietal pain is not restless, but is in fact scared to move for fear of worsening the pain.* Any pressure on the peritoneum will cause the pain to increase.

Peritoneal pain is produced by noxious stimuli to the parietal peritoneum. It usually lateralizes due to afferent neurons from the peritoneal surface that travel to the spinal cord only on the side of the body that serves the adjacent subcutaneous tissue or skin dermatome. This permits intense, well-localized pain in the abdominal area immediately adjacent to the site of peritoneal irritation.

The *intensity of the pain* depends upon the nature and quantity of the irritant. A small amount of acid or bile leaking into the peritoneum will cause more irritation than a larger amount of neutral material and enzymatically active substances are more irritating than non-active substances. Thus, blood, urine, and even bacteria are not easily detected in very small amounts.

**Basic Approach to Establishing the Diagnosis**

- The history will provide the most important clues to the etiology of the abdominal pain
- Combining physical examination with the clues from the history will give the diagnosis in the majority of cases of abdominal pain
- Labs and radiology can be used to help confirm or rule-out diagnoses

*What additional history and/or physical examination information will help you establish the diagnosis?*

**I. History** – the history determines the direction of the investigation

**Location:** Ask the patient: “Please show me where you feel the pain”
Watch the patient’s hand as they point to the spot. This may occur in a characteristic fashion that will help you locate the source of the pain. Those with parietal pain may point with a single finger to the pain whereas those with visceral pain often use their palm to show you a general area that hurts.

**Quality:** Ask: “What does it feel like: dull, burning, cramping, aching, or sharp like a knife?”

- *Squeezing, cramping, or colicky:* suggests pressure buildup and release inside a hollow organ such as the gallbladder, bile duct, ureter, the intestines, or the uterus
- *Aching:* suggests a solid organ as such as the liver or pancreas
- *Hot or burning:* suggests an irritated nerve
- *Gnawing or sour:* suggests mucosal origin such as inflammation from ulcers or esophagitis

**What if the patient described pain that radiated to the back?**

**Radiation:** Ask the patient: “Do you feel the pain moving anywhere else?”

Characteristic sites of radiation may suggest the source:

- *Pancreatic head:* midepigastric pain radiating to the mid back
- *Jejunum and proximal ileum:* periumbilical pain radiating to the mid back
- *Gallbladder:* epigastric pain radiating to right scapula or shoulder
- *Diaphragm:* pain in the supraclavicular area in the area of the trapezius muscle
- *Aorta:* periumbilical pain radiating to the mid back
- *Uterus:* low mid-abdominal pain radiating to the low back
- *Ureter:* lower quadrant pain radiating to the genitals, or inner thigh

**Clue:** Palpation over the area of referred pain does not increase the pain. It may relieve it.

**Duration:** Ask the patient: “When do you get the pain and how long does it last?”

- *Periodic discomfort:* suggests obstruction of hollow viscera.
- *Constant pain:* suggests malignancy
- *Absence of pain while asleep:* suggests a functional disorder
- *Pain directly after a meal:* suggests a gastric ulcer
- *Pain when stomach is empty:* suggests duodenal ulcer or pancreaticobiliary disease

Clue: food decreases pain from duodenal ulcers and increases pain from gastric ulcers.

**Aggravating/Relieving Factors:** Ask the patient: “Does anything make the pain better or worse?”
Examples: eating, drinking, specific foods, bowel function, body position, effect of coughing or deep breathing, sleep, effect of medications

**Associated Symptoms and Signs:** Ask the patient about each of these:

- weight loss, change in bowel habits, blood in the stools, yellowing of the skin (jaundice), bloating, belching, fevers, chills, nausea, vomiting

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II. **Physical Exam – the exam furnishes the definitive data**

**General:**

The abdominal cavity encloses many organs that may be involved in a host of different disease processes. Inflammation of the visceral peritoneum results in abdominal pain that cannot be localized by the patient. Only when inflammation reaches the parietal peritoneum, does the pain occur in the area of inflammation. A careful history and the abdominal exam are critical to determining the source of a patient's complaint.

In order to avoid failing to perform a complete and thorough assessment, the exam should be performed in an organized and consistent fashion. The sequence of the physical exam of the abdomen should be as follows: (1) inspection, (2) auscultation, (3) percussion, and (4) palpation.

Patients should be examined in a warm room. By convention, the examiner stands at the patient's right side. A chaperone should be available for the comfort of the patient and the legal protection of the examiner. The patient should be draped with a sheet or blanket covering the lower limbs up to the symphysis pubis. The breasts should be covered.

Initially, the patient should be lying supine in a comfortable position so that the abdominal wall is flattened. This is the best position for inspection and auscultation. Auscultation should be performed before percussion or palpation, as these may stimulate bowel sounds. Increased bowel sounds may obscure vascular bruits.

A relaxed abdomen helps percussion and palpation. Following inspection and auscultation, the patient should be placed in a slightly flexed position at the waist in order to reduce the tension on the abdominal wall. Slightly raise the head of the bed, and ask the patient to bend both knees.

**Inspection** - Positioning a light so it shines down over the patient and casts a shadow on the abdominal wall will highlight asymmetry of the abdominal wall.

- Look for enlargement of the gallbladder, visible loops of bowel distended by ileus or obstruction.
- In adults, prominent peristaltic waves of contraction may be seen in patients with partial or complete small intestinal obstruction.
- Caput Medusa (prominent veins on the anterior abdominal wall that radiate away from the umbilicus like the spokes of a wheel) denotes portal venous hypertension.
- Abdominal scars – Can signify potential surgical adhesions as contributing factors. You should account for all abdominal scars in the history.

**Auscultation**

- RUQ – listen for friction rubs (always pathologic) and bruits (10-50% of hepatic malignancies will have one)
- Epigastric region - bruits from the aorta, celiac axis, or superior mesenteric artery, or the continuous venous hum from portosystemic shunting
- Flanks - bruits suggesting renal artery stenosis
- Bowel
  - considered absent if none are heard over a period of 5 minutes
  - hyperactive with high pitched gurgles and rushes in intestinal obstruction
  - hypoactive is soft and low tone sounds which can be heard in ileus

**Percussion** - if a patient is experiencing pain, it is best to begin the exam in an area distant from the location of the pain

- Peritoneal inflammation is detected if light percussion elicits peritoneal signs
  - this method is more sensitive and humane than palpation first
- Determine if the liver or spleen is enlarged before attempting to palpate the organs
- Ascites causes shifting dullness if >500 cc is present in the intra-abdominal cavity
- Watch the patient's face for signs of grimacing, especially significant if it occurs even though the patient was intentionally distracted by conversation or questions

**Palpation** - Performed last but probably the most important part of the exam

- Palpate all quadrants lightly, then repeat with deep palpation
- In an anxious patient or suspected factitious pain, palpate the abdomen with the diaphragm of a stethoscope while pretending to listen
- Placing the patient’s hand against the examiner's hand during palpation will help the ticklish patient
- To differentiate an enlarged left lobe of the liver from splenomegaly, remember that the liver moves down during respiration. The spleen moves down and medially
- Pay particular attention to referred rebound - when the examiner palpates deeply and "lets go" - referred rebound occurs when the patient perceives pain at another site
- Referred rebound tenderness is almost always an ominous sign that indicates the presence of peritonitis or peritoneal irritation

18:8
- Rectal examination is important on all patients with abdominal pain, and pelvic exam should be considered on all sexually active female patients
- Be aware of abdominal wall pain as an entity and how to distinguish this from underlying intra-abdominal sources of pain. Tensing the abdomen with a partial sit-up/crunch will protect an underlying organ from the examiner’s hand during palpation. In contrast, if palpating the area of tenderness results in more pain during the crunch, there is a high likelihood of an abdominal wall etiology. This is known as Carnett’s test.

General Comments

Remember that the abdomen has a back. The abdominal exam is not complete until the back has been examined. This is important because the discomfort from many disorders that originate in the back may be perceived in the abdomen. Look for scoliosis, evidence of trauma, vertebral tenderness, evidence of degenerative disease, or a rash consistent with shingles. These radicular-based symptoms may be perceived as anterior abdominal wall pain. Assess if there are any postures or positions that may provoke the patient's pain. Consider the possibility of thoracic disease in every patient with abdominal pain.

How can laboratories and radiographs help you with the evaluation of her abdominal pain?

III. Laboratory and Radiology – can at times help establish the diagnosis

Laboratories: Blood, Urine, and Stool Studies:

**Complete blood count (CBC)**
- White cell count – high neutrophil level suggests bacterial infection
- Hematocrit – low level indicates blood loss, low production, or hemoconcentration
- Platelets – low level indicates destruction, sequestration (spleen), or low production

**Amylase and lipase** will help identify pancreatitis (elevated in acute pancreatitis)
- Lipase is more specific for acute pancreatitis.

**Liver associated enzymes**
- AST, ALT—hepatocellular injury
- Alkaline phosphatase, GGT, bilirubin – cholestasis
- Protein, albumin, and PT/INR – reflects the synthetic function of the liver
Urinalysis

White cells may indicate infection
Red cells may indicate infection, stone, or cancer

Stool studies – Rarely indicated in the absence of diarrhea. If an iron deficiency anemia is present, fecal occult blood can be tested.

β-HCG – pregnancy test (Qualitative = positive/negative)
**Radiology and other ancillary diagnostic studies:**

**Kidney-Ureter-Bladder (KUB)/Upright plain film** - X-ray of the abdomen shows air-fluid levels in obstruction. The upright film checks for free-air under the diaphragm (a sign of perforation). Some physicians use a chest x-ray (PA) to check for free air.

**Barium swallow or Barium enema** - The barium shows up bright white on x-ray and can help to show a mass or ulcer in the stomach, small intestines, or colon/rectum. It can also show luminal narrowing or evidence of strictures. This is an older test and is not used as often anymore.

**Abdominal ultrasound (U/S)** - very useful for many parts of the abdomen. RUQ U/S can show liver parenchymal abnormalities/masses, gallstones or biliary ductal dilatation. Kidney U/S can evaluate for hydronephrosis, size, scarring, and cysts. Pelvic U/S can evaluate the uterus and ovaries.

**CT Scan** - Shows detailed information about the structure of the abdomen. CT can be done without contrast dye or with oral and/or IV contrast dye depending on the indication.

**HIDA Scan** - a nuclear medicine study which gives information about the function of the biliary system and limited anatomical information.

**Magnetic Resonance CholangioPancreatography (MRCP)** - Radiology software creates a three dimensional image of the biliary and pancreatic ductal system. Non-invasively gives similar information as ERCP but without the ability for further diagnostic and therapeutic procedures such as stenting, biopsy, and stone extraction.

**Percutaneous Transhepatic Cholangiography (PTC)** – Interventional radiologist injects dye into the biliary tree by putting a needle through the abdominal wall. This does allow for procedures such as stenting or dilatation of a duct, particularly when the papilla cannot be accessed endoscopically.

**Esophago-Gastro-Duodenoscopy (EGD)** – An endoscopist passes a small flexible tube though the mouth and can see the esophagus, stomach, and proximal duodenum. Patient is moderately sedated. Can obtain biopsies or perform hemostasis of bleeding lesions. Dilation and or stenting can be done for luminal strictures in the esophagus or pylorus (transition point between stomach and duodenum).

**Small Bowel Enteroscopy** - similar to EGD but goes farther – esophagus to the proximal to mid jejunum. A particular endoscope (single or double balloon enteroscope) can reach the distal jejunum or proximal ileum in some cases.

**Endoscopic Retrograde CholangioPancreatography (ERCP)** – A specialized upper endoscope is passed down from the mouth into the stomach through the pylorus into the duodenum to the ampulla of Vater. Then the endoscopist may place a catheter into the biliary or pancreatic duct and inject dye showing detailed anatomic information. Procedures that can be done at the time of ERCP include stone removal, sphincterotomy, duct stenting, and biopsies.
*Endoscopic Ultrasound (EUS)* – scope similar to EGD modified at the distal tip with an ultrasound processor. Obtains high resolution pictures of the wall of the intestinal tract, liver, gallbladder, and pancreas. Can be used to assess for gallstones within the common bile duct without the need for ERCP. Also used for staging GI malignancies, obtaining fluid and tissue samples of organs adjacent to the luminal GI tract (e.g. liver, pancreas, lymph nodes, etc.).

*Flexible Sigmoidoscopy* (Flex-Sig) - a scope is placed through the anus to visualize the rectum, sigmoid, and distal descending colon. The physician can endoscopically assess the mucosa checking for evidence of any inflammation, malignancy, hemorrhoids, or fissures.

*Colonoscopy* – similar to sigmoidoscopy but goes farther – from anus to cecum and terminal ileum.
The next section will outline classic presentations of common causes of abdominal pain. This section will help you develop basic illness scripts for these disorders and key findings are outlined in figures for each diagnosis.

1. **Inflammatory Bowel Disease – Ulcerative Colitis and Crohn’s Disease**

   **Background:**
   Inflammatory Bowel Disease (IBD) is idiopathic and chronic
   Differentiating Ulcerative Colitis from Crohn’s Disease - not possible in 10-15%
   Peak age of onset: 15-30 years old with 2nd Peak: 60-80 years old
   Male: Female ratio 1:1
   Special Populations: 2-4 fold increase in Jewish population in U.S.

**Ulcerative Colitis:**
- **History:** Recurrent diarrhea, rectal bleeding, mucus, tenesmus, crampy abdominal pain
- **Physical Exam:** tender anal canal and blood on rectal exam. May be tender on palpation over colon. If perforation has occurred – peritonitis.
- **Labs/Radiology and other Tests:** Negative stool for bacteria, *C. difficile*, ova and parasites. Sigmoidoscopy/colonoscopy shows inflammation and ulceration of the mucosa beginning at the rectum and extending proximally, towards the cecum. Histology shows crypt distortion, cryptitis, crypt abscess.
- **Diagnosis:** Based on history & exam, confirmed by colonoscopy and histopathology.

**Crohn’s:**
- **History:** predilection for distal small bowel or proximal large bowel but can occur anywhere from mouth to anus. Recurrent episodes of RLQ pain and diarrhea. Can mimic acute appendicitis. Fibrotic stenosis can lead to intermittent colicky pain occasionally accompanied by nausea and vomiting.
- **Physical Exam:** Tender RLQ with palpable mass during obstructive episodes, fever, fistulas.

- **Labs/Radiology and other Tests:** Leukocytosis, Endoscopy/Colonoscopy may show rectal sparing, skipped lesions of aphthous ulcerations, and inflammation.

- **Diagnosis:** Clinical (history and physical), confirmed by endoscopy/colonoscopy and histopathology.
2. **Peptic Ulcer Disease (PUD)**

**Background**

Definition: > 5 mm break in the gastric or duodenal mucosa. Peak age of onset: 6th decade of life

Male slightly more common than females

Special Populations: NSAID use, Helicobacter pylori infection, Zollinger-Ellison (rare)

- **History:** Burning or gnawing epigastric discomfort, can be ill-defined aching sensation or hunger pang. Gastric Ulcer (GU) pain may be precipitated by food and have nausea and weight loss. Duodenal Ulcer (DU) most common 1.5-3 hours after a meal, and is relieved by antacids or food. 2/3 of patients have pain that wakes them from sleep between midnight and 3 am when acid secretion increases. Alternatively, may present with melena and signs of blood loss when the ulcer has eroded to a blood vessel.

- **Physical Exam:** Minimal findings. A severely tender, board-like abdomen suggests perforation.

- **Laboratory/Radiology and Other Tests:** EGD
  - Fasting gastrin > 150 pg/mL in Zollinger-Ellison Syndrome (ZES)*
  - Serum IgG, stool antigen, or urea breath test to assess for Helicobacter pylori

- **Diagnosis:** Clinical (history and physical) and EGD

*Note gastrin may also be elevated due to proton pump inhibitor use, however it rarely rises above 1,000 pg/ml with PPIs. Ideally, these should be held for 1-2 weeks prior to testing.
3. **Pancreatitis**

**Background:**
- Two forms: acute and chronic
- Spectrum varies from mild to necrotizing
- Common causes: gallstones, alcohol, hypertriglyceridemia, post-ERCP, trauma, post-operative, drug related, and sphincter of Oddi dysfunction.

- **History:** Steady, boring pain in epigastrum and periumbilical area, radiates to the back. Pain worse lying flat, better with sitting with knees flexed. Pain may vary from mild to intolerable.
- **Physical Exam:** Patient in distress with signs of shock if pancreatitis is severe. Tenderness and muscle rigidity are variable. Bowel sounds diminished or absent. 10-20% with pulmonary findings. Severe necrotizing pancreatitis may give Cullen’s sign (periumbilical discoloration) or Grey-Turner’s sign (discoloration of the flanks).
- **Laboratory/Radiology and Other Tests:** Serum amylase and lipase elevation
  - CT scan is helpful if the diagnosis is in question or if the pancreatitis does not improve with treatment.
  - HIDA scan help evaluate the gallbladder and biliary tree (not typically required in acute pancreatitis)
  - Elevated bilirubin or AST/ALT suggests gallstones as the etiology. An ALT level 3x upper limit of normal is 95% sensitive for gallstone pancreatitis.
- **Diagnosis:** Clinical (history and physical), confirmed by amylase/lipase
  - Scoring systems used to assess patient’s risk of dying: Ranson, Imrie, BISAP and Apache II
4. **Cholecystitis**

**Background**
- Two stone types – Cholesterol stones comprise 80%; Pigmented stones 20%
- At autopsy: 20% of females have gallstones, 8% of males
- Special Populations: First-degree relatives of gallstone carriers, American Indians (Pima), Chilean Indians, and Chilean Hispanics are at high risk of developing gallstones
  - Diabetic patients may not sense the pain as much and present with gangrene

- **History:** Severe steady ache in epigastrum or RUQ that starts suddenly and persists with severe intensity. May be precipitated by fatty or large meal. Pain may radiate to the right shoulder or scapula. Nausea and vomiting frequently seen. 60-70% of patients report prior attacks that spontaneously resolved within hours of onset.

- **Physical Exam:** Tender RUQ and fever, *Murphy’s sign* (Gently palpate the RUQ, ask the patient to take a deep breath, when an inflamed gallbladder comes in contact with your fingers, the patient will have an “inspiratory arrest”- stop breathing to stop the pain), *Courvoisier’s sign* (palpable distended gallbladder in the RUQ) generally indicates malignancy, clinical jaundice should prompt a search for a common bile duct or cystic duct stone.

- **Laboratory/Radiology and Other Tests:** Leukocytosis (Elevated WBC’s), may have mild bilirubin elevation, aminotransferases (AST and ALT) mildly elevated <5 times the normal.
  - RUQ ultrasound will show stones in the gallbladder >90% of patients
  - HIDA scan help evaluate the gallbladder and biliary tree

- **Diagnosis:** Clinical (history and physical), labs, plus RUQ ultrasound
History
• RUQ pain precipitated by large or fatty meal

Physical Exam
• RUQ tenderness, Murphy's sign

Labs/Radiology
• Elevated WBCs, mildly elevated AST/ALT, RUQ US

Diagnosis
• Cholecystitis
5. **Appendicitis**

**Background**
- Lower incidence in under-developed countries and in lower socioeconomic groups
- Peak age of onset: second and third decade of life, rare in very young or very old
- Male: Female ratio 1:1 except between puberty-25y/o Male: Female 3:2
- Special populations: Perforation most common in infancy and advanced age

- **History:** Initially, poorly localized periumbilical or epigastric abdominal pain, not relieved by defecation or flatus. Pain is mild, cramping, and not catastrophic. After 4-6 hours, pain becomes more severe, steady, aggravated by motion or cough and starts to localize in RLQ. Anorexia is always present, may have nausea/vomiting. After 24 hours, increased likelihood appendix has ruptured.

- **Physical Exam:** Findings vary with time and anatomical location of appendix. Tenderness, rebound tenderness, and referred rebound tenderness are often (not always) present. Flexion of the right hip will cause guarding when the parietal peritoneum is involved. Temperature > 101° F or 38.3° C suggests perforation. *Obturator sign* (pain with right hip flexion and internal/external rotation) and *Psoas sign* (pain with resisted extension of right leg) may be present.

- **Laboratory/Radiology and Other Tests:** Leukocytosis usually present, WBC>20,000 suggests perforation
  - U/S shows enlarged thick-walled appendix. Can rule-out other causes
  - CT scan shows non-filling with contrast, adjacent inflammatory changes and thickness >6mm

- **Diagnosis:** Clinical (history and physical) and confirmed with imaging
6. **Viral Gastroenteritis**

**Background**
- When an acute appendicitis with rupture has been missed, gastroenteritis is the most common previous “working diagnosis”
- Affects all ages and is worldwide
- Special Populations: Young children and the elderly at risk for complications

- **History:** Sudden onset crampy abdominal pain, vomiting common in children, diarrhea common in adults. Anorexia, malaise, headache, fever, and myalgias. Patient may have a known sick contact in family, school, or friends. Incubation period 12-72 hours.
- **Physical Exam:** Fever, borborygms, abdomen tense but relaxes between cramps, lack of tenderness on rectal exam, absence of psoas sign (see appendicitis).
- **Laboratory/Radiology and Other Tests:** White count normal or slightly elevated with lymphopenia (low lymphocyte count), does not have left shift (that is no “bands” - immature neutrophils)
- **Diagnosis:** Clinical (history and physical)
7. Acute Intestinal Obstruction

Background:

Can be caused by mechanical or non-mechanical (neuromuscular)

Mechanical Risk factors:
- **extrinsic factors** - adhesive bands from prior surgeries, hernias
- **intrinsic factors** - carcinoma, diverticulitis
- **luminal factors** – gallstones, volvulus, intussusceptions

Neuromuscular Risk factors:
- **Adynamic ileus** – occurs after any peritoneal insult
  (surgery, chemical insult, thoracic disease)
- **Spastic or Dynamic ileus** – result of extreme or prolong contraction
  (heavy metals, uremia, porphyria, intestinal ulcers)

- **History**: Pain, vomiting, obstipation
- **Physical Exam**: Abdominal distention, tenderness and rigidity may be minimal, signs of shock appear late in the course
- **Laboratory/Radiology and Other Tests**: elevation in amylase, leukocytosis, X-rays may show air-fluid levels, CT scan may be necessary in small bowel strangulation
- **Diagnosis**: History, physical, labs, plus radiology
8. **Acute Intestinal Ischemia (Mesenteric Ischemia)**

**Background:**

Ischemia may result from arterial occlusion (most common), vasospasm, or veno-occlusion
Mortality rate > 50%
Risk Factors: atrial fibrillation, recent myocardial infarction (heart attack), valvular heart disease, or recent cardiac catheterization or vascular catheterization
Special populations: Hypercoagulable state – protein C or S deficiency, Factor V Leiden deficiency, antithrombin III deficiency, polycythemia vera, or carcinoma

- **History:** Severe, acute pain out of proportion to the physical exam findings, may have nausea/vomiting, diarrhea, bloody stools
- **Physical Exam:** early in the course the exam is unimpressive, later peritoneal signs develop – rebound tenderness
- **Laboratory/Radiology and Other Tests:** plain film may show bowel edema "thumb printing", three-dimensional CT shows ischemia, angiography
- **Diagnosis:** History, physical, CT, angiography, laparotomy
9. **Pelvic Inflammatory Disease**

**Background:**

**Definition:** Infection that ascends from the vagina to involve the endometrium and/or fallopian tubes  
Peak age of onset: 15-25y/o  
Causative Agents: Most often associated with Chlamydia and Gonorrhea  
Risk Factors: Sexually active females with endocervical infection or bacterial vaginosis, history of salpingitis or recent vaginal douching, use of IUD, multiple sexual partners

- **History:** Dull or aching midline abdominal pain with abnormal vaginal bleeding (endometritis) or lower abdominal pain with nausea, vomiting, and peritonitis (salpingitis), 3-10% with RUQ pain
- **Physical Exam:** Yellow cervical discharge and cervical motion tenderness, fever (1/2 of patients), may have palpable adnexal mass if tubo-ovarian abscess present
- **Laboratory/Radiology and Other Tests:** May have elevated WBC’s, AST/ALT normal, positive GC/Chlamydia testing (not immediately available), check β-HCG to rule-out ectopic pregnancy, check urinalysis and culture
- **Diagnosis:** History, physical, confirm with labs
10. Irritable Bowel Syndrome (IBS)

Background
Definition: Altered bowel habits and abdominal pain or discomfort without detectable structural abnormality.
Peak age of onset: most patients diagnosed before age 45
Females>Males (2:1) Women are 80% of “severe” IBS
High prevalence of comorbid psychiatric conditions, especially anxiety and depression
May be associated with childhood sexual abuse

- **History:** Abdominal pain variable in intensity and location, frequently episodic and crampy, may have a background of constant ache. Pain often exacerbated by eating or emotional distress and is relieved by flatus or stools. May have diarrhea, constipation, or an alternating form in which both are present at various times.

- **Physical Exam:** Benign (normal)

- **Laboratory/Radiology and Other Tests:** Limited evidence to support specific routine testing in patients without alarm features (weight loss, rectal bleeding or nocturnal pain). Routine screening labs are typically normal (CBC and chemistries). Diarrhea predominant IBS consider screening tests based on patient’s clinical history. Some patients with alarm features may require more extensive testing to rule out other disorders.

- **Diagnosis:** Entirely Clinical
  - Rome III Criteria can be used to make the diagnosis
    - Recurrent abdominal pain or discomfort at least 3 days a month in the last three months associated with two or more of the following:
      - Improvement with defecation
      - Onset associated with change in frequency of stool
      - Onset associated with a change in form (appearance) of stool
Summary

The cause of abdominal pain can usually be discerned from a careful history and physical exam. As in many causes of pain, eliciting the location, quality, radiation, duration, and exacerbating/relieving factors give essential clues to the etiology. Pain from an organ tends to be perceived as mid-line whereas pain from the organ capsule tends to lateralize. The patient with organ pain tends to be restless and cannot clearly pinpoint the source. Alternatively, pain from the peritoneum tends to be precisely localized and the patient is usually very still, with any movement causing increased pain.

The physical exam then builds on the history. The sequence of the physical exam of the abdomen should be as follows: (1) inspection, (2) auscultation, (3) percussion, and (4) palpation. A rectal exam should be performed on all abdominal pain patients and consideration should be given to a pelvic exam for sexually active female patients. Combining physical exam findings with the clues from the history will usually give the diagnosis.

Labs and radiology are adjuncts used to confirm the diagnosis. A pregnancy test should be standard in any female of reproductive age with acute abdominal pain.

Review the common causes of abdominal pain that you undoubtedly will see during your clerkship years and future practice. An additional schema is shown below to assist you in establishing the diagnosis.
Returning to our first patient …

The historical clues with this patient should lead the reader to consider gallstone disease above other etiologies. The risk factors of female, fertile, and >forty years of age raise the risk for cholelithiasis (gallstones in the gallbladder). The patient’s description of pain is colicky in nature which is consistent with gallstones as well. The pain is typically from intermittent passage of stones into the common duct or from partial occlusion of the cystic duct/gallbladder neck with resultant spasm/distention of the gallbladder itself. While anti-inflammatory medications (NSAIDs) may have some utility, Tylenol (acetaminophen) does not appear to offer durable or lasting relief. Once a stone remains in the common bile duct (choledocholithiasis), the patient may develop ascending cholangitis from obstruction of the common bile duct. If the stone is impacted at the cystic duct (acute cholecystitis), the gallbladder becomes infected and the vague, non-lateralizing pain typical of pain from a hollow viscus evolves to the steady, persistent right upper quadrant parietal type pain. This may be accompanied by fever (often less than 102 F), and nausea and vomiting, which usually follow the abdominal pain. Laboratory tests should be obtained to assess for evidence of infection (WBC) and liver associated enzymes (LAEs) to assess for hepatobiliary obstruction/inflammation. The first imaging test to obtain is the RUQ US as it is readily available, least expensive and able to rapidly triage for the presence of acute cholecystitis (thickened GB wall, pericholecystic fluid) and stones. If jaundice is present along with RUQ pain and fever (Charcot’s triad), then ascending cholangitis becomes likely. A normal RUQ US does not exclude this and an endoscopic US or MRCP have a much higher accuracy.
rate. If a stone is found to be obstructing the common bile duct, then an ERCP should be performed for drainage of the infected bile under pressure. When a stone is impacting the distal common bile duct, gallstone pancreatitis may occur and patients may describe the pain as radiating to the back.

Returning to our second patient……

Our second patient has a clinical presentation which suggests small bowel obstruction. Important historical information would include surgical history as adhesions are the most common cause of small bowel obstruction in adults. Other causes of intestinal obstruction are volvulus, hernias, and malignancy. This patient had a total abdominal hysterectomy for menorrhagia secondary to uterine fibroids and an appendectomy as a teenager. Other important questions to ask include whether she is passing gas (obstipation) or stool (constipation). It is important to ask about the description of the emesis. If she describes it as biliary/green in color, then the obstruction may be proximal. If the emesis is feculent, then the obstruction is likely distal. Initial labs should include a CBC and basic chemistry panel. The CBC may show a slight leukocytosis. Small bowel obstructions may alter electrolytes as well and can show impaired renal function. With vomiting, hypokalemia may ensue. A lactic acid level is important to check and if elevated may suggest bowel ischemia or even necrosis. A KUB is an important initial test to order which can confirm the diagnosis, possibly localize to the small bowel or colon, and provide evidence of partial versus complete obstruction. The KUB will likely show dilated loops of small bowel in this patient. A CT is more accurate than a KUB and allows complete assessment of the abdomen. Initial management is supportive and includes bowel rest, placement of a nasogastric tube for decompression, administration of IV fluids, and repletion of electrolytes.

Your next patient (abdominal pain in pediatric population)…

A mother brings her 18-month-old son to your clinic stating “he has been acting really sick.” She states he has periods where he is incredibly fussy and seems to be in severe pain, though she can’t tell exactly where the pain is coming from. When he’s not fussy and irritable, he seems to be lethargic and “out of it.” He has not had any URI symptoms, he has been afebrile, and before this episode started earlier today, he had been in good health. His birth history is unremarkable, he has been growing and developing appropriately, and his immunizations are up to date. He hasn’t wanted anything to eat or drink today. “Oh, and one more thing,” the mom adds. “He’s had a couple of small, funny poops today. They almost look jelly-like.”

Abdominal pain is a very common presenting symptom in pediatrics. The approach to a child with abdominal pain is very similar to the approach to abdominal pain in adults, and many of the same algorithms presented in this chapter apply to children. Keep in mind, infants and toddlers with abdominal pain can’t tell you what’s bothering them, and often present with fussiness, irritability, or simply ‘not acting right.’ School-aged children may just complain of a “tummy
ache” and may have difficulty localizing the pain or specifying the characteristics of the pain. Associated symptoms may help provide clues, so it is important to ask about vomiting, diarrhea, constipation, appetite, and fever. As with adult patients, adolescents should be questioned privately about their sexual behaviors.

The approach to abdominal pain in children differs significantly depending on the whether the pain is acute or recurrent (chronic). While most of the disease processes that cause acute abdominal pain in adults can also cause acute abdominal pain in children, there are a couple that warrant additional mention. An incarcerated hernia, seen most commonly in the first year of life, may present with fussiness, vomiting, and generalized abdominal pain. Another surgical emergency, malrotation with midgut volvulus, often presents in the neonatal period with bilious emesis.

Intussusception is another cause of acute abdominal pain affecting children most commonly between the ages of 6 months and 3 years of age. Irritability, often intermittent, with periods of normal behavior between episodes of pain is common. Patients may also present with lethargy or mental status changes. The classic ‘currant-jelly’ stool is often a late finding if present at all. In a patient with suspected intussusception, an air-contrast or barium enema is the diagnostic modality of choice, and is often therapeutic as well as diagnostic. While a Meckel diverticulum is a common lead point for intussusceptions in younger children, lymphoma is common in older children with intussusception and patients should be evaluated accordingly.

Recurrent abdominal pain is a common problem in children, affecting more than 10% of children at some time during childhood. Peak incidence is seen in elementary and middle-school children. Constipation is the most common cause of recurrent abdominal pain in children, but peptic ulcer disease, chronic gastritis, and inflammatory bowel disease can also present during childhood. Functional abdominal disorders, including Irritable Bowel Syndrome (IBS), are those not caused by organic disease, and can be frequently seen in children. Functional abdominal pain, which differs from IBS in minor ways, is seen fairly commonly in children, and presents with pain that characteristically occurs daily or nearly every day, and is associated with an impairment in their ability to function normally (i.e. go to school). The pain tends to be worse in the morning before going to school, particularly following a weekend or vacation. While functional abdominal pain is a diagnosis of exclusion and other disease processes need to be ruled out, care should be taken to not order too many tests and studies as this may actually compound the problem. Treatment of functional abdominal pain can be complicated, and specific attention needs to be paid to the psychosocial triggers.

Already concerned for acute abdominal pain in this patient, you proceed to your physical exam where you find a lethargic toddler lying in mom’s arms. He is slightly tachycardic and on palpation of his abdomen, you think you might feel a ‘sausage-like mass.’ You are immediately
concerned for intussusception and send him for an air-contrast enema. The radiologist confirms
the diagnosis and the intussusception is reduced during the procedure.
Practice questions (and answers):

1. Which of the following historical features is not consistent with a diagnosis of Pelvic Inflammatory Disease (PID)?
   a) RUQ pain
   b) Vaginal bleeding
   c) Rectal bleeding
   d) Temperature of 101°F

2. Which of the following physical signs is associated with acute appendicitis?
   a) Cullen’s sign
   b) Obturator sign
   c) Chandelier sign
   d) Murphy’s sign

3. Which of the following causes of abdominal pain are more likely to present as parietal pain?
   a) Cholelithiasis
   b) Nephrolithiasis
   c) Appendicitis
   d) Peptic ulcer disease

4. Which of the following is not a risk factor for the development of gallstones?
   a) Ethnicity
   b) Pregnancy
   c) Weight loss
   d) Hypercholesterolemia
Answers:

1. c) Rectal bleeding

RUQ may be seen in 3-10% of patient with PID, often associated with involvement of the liver capsule (Fitzhugh-Curtis syndrome). Vaginal bleeding and fever are common in this condition. Rectal bleeding should prompt the search for alternate cause as this is not associated with PID.

2. b) Obturator sign

When the appendix lies against the obturator internus muscle, engagement of the muscle by right hip flexion and internal rotation may worsen the pain of acute appendicitis (obturator sign). Cullen’s sign is periumbilical ecchymosis associated with hemorrhagic pancreatitis. Chandelier sign is another name for cervical motion tenderness associated with PID. Murphy’s sign is the halting of inspiration during RUQ palpation associated with acute cholecystitis.

3. c) Abdominal pain can be classified as visceral, parietal, or referred. Visceral pain is usually experienced when there is inflammation of a hollow organ secondary from noxious stimuli triggering visceral pain receptors. This pain can be described as dull, gnawing, burning and cramping. Examples of visceral type pain include cholelithiasis, nephrolithiasis, and peptic ulcer disease. In contrast, parietal type pain results from direct stimulation of the peritoneum and is generally more intense and precisely localized than visceral pain. An example of parietal pain is acute appendicitis.

4. d) Gallstone disease is one of the most prevalent diseases in the United States. Several risk factors exist for the development of gallstones. Ethnic predisposition has been reported in Pima Indians and Scandinavians. During pregnancy, bile becomes more lithogenic and may be related to an increase in circulating estrogen which stimulates cholesterol secretion. Another reason pregnancy predisposes to gallstones is from hypomotility of the gallbladder and bile stasis. Rapid weight loss also leads to the development of gallstones in approximately 25% of patients. During caloric restriction, hepatic cholesterol secretion increases. Hypercholesterolemia is not a risk factor for gallstones, although hypertriglyceridemia is. An inverse relationship exists between serum HDL and the presence of gallstones.
ICR Abdominal Pain Cases

The small group cases for this session will be the 3 patients that you will discuss as part of your Integrated Clinical Skills (ICS) experience on this topic.

Please complete the form on the next page for the patient that you wrote up during your ICS session.

Please be prepared to give a 3 to 5 minute presentation of this patient for your ICR session. Your ICR preceptor will ask for someone to present each of the three cases.
Summary statement (1-3 sentences)

Prioritized problem list

1.
2.
3.
4.
5.
6.

Prioritized differential diagnosis (include at least 3 diagnostic options)

1.
2.
3.
4.
5.

Justification for leading diagnosis (history and physical exam findings and any ancillary data provided; write as a paragraph):

Plan (diagnostic work-up and/or therapeutic)

1.
2.
3.
4.
Introduction to Clinical Reasoning:
Hypercalcemia and Hypocalcemia

Steven Brietzke MD
Babette Glister, MD

For each patient, use the same questions below:

1. A 19-year-old woman presents for an induction physical prior to Army basic training. She is asymptomatic and her physical examination is normal. Routine laboratory testing identifies a calcium level of 11.1, with no other abnormalities seen on a complete metabolic panel, complete blood count, or routine urinalysis.

2. A 23 year-old male presents after successfully completing basic training. He reports abrupt-onset colicky right flank pain radiating to the groin and new gross hematuria on one occasion. He is otherwise healthy with a normal physical examination. Routine laboratory testing reveals a serum calcium of 11.5, a serum phosphorus of 5.0, with otherwise normal metabolic panel and complete blood count. Urinalysis confirms RBCs and blood without other abnormalities.

Questions:
1. What other questions should you ask?
2. What additional laboratory testing should you obtain?
3. What causes of hypercalcemia should you consider?
4. Should he/she be allowed to enter the military?

Objectives: At the end of the session, students will be able to:

1) Understand the use of PTH in the differential diagnosis of hypercalcemia (key step = PTH dependent or independent)
2) Recognize and contrast typical laboratory patterns (PTH, serum calcium and phosphorus, urinary calcium) in the following disorders:
   - Primary hyperparathyroidism, familial hypocalciuric hypercalcemia,
   - hypercalcemia of malignancy, Vitamin D related hypercalcemia (i.e. hypervitaminosis D deficiency
3) Recognize the typical clinical presentations and laboratory findings for hypocalcemia: pseudohypocalcemia, hypoparathyroidism, or non parathyroid conditions (vitamin D deficiency or impaired vitamin D formation or action)

Overview:
This section will discuss the approach to calcium disorders. Emphasis will be placed on pathophysiology, and in particular, the central role of PTH. Both rules of thumb (heuristics) as well as algorithmic (schema) approaches to establishing the diagnosis of calcium disorders will be presented. Additionally, prototypic presentations of common diagnoses (key findings and basic illness scripts) will be discussed.
Basic Science Highlights

The dominant hormonal control of serum calcium is PTH. There is normally a delicate equilibrium between serum ionized calcium and PTH production by the parathyroid gland, such that:

- A small **decrement** in serum ionized calcium **stimulates** PTH release
- A small **increment** in serum ionized calcium **suppresses** PTH release

**Actions of PTH on Calcium Homeostasis:**

**Direct Effects**
- Stimulate osteoclast-mediated release of calcium from bone
- Decrease renal calcium clearance (increase tubular reabsorption calcium from glomerular filtrate)
- Stimulates renal 1-alpha-hydroxylase to convert calcidiol into the far more potent calcitriol, which in turn enhances gut absorption of calcium.

**Indirect Effects**
- Promotes intestinal absorption of calcium (an effect directly attributable to calcitriol)

Thus, directly or indirectly, PTH profoundly enhances ALL routes of influx of calcium into the system, and opposes ALL routes of egress. It is the Big Kahuna! As we will see, the differential diagnosis of hypercalcemic and hypocalcemic disorders hinges on the assessment of whether PTH is behaving appropriately or inappropriately.

**Other Actions of PTH:**

Aside from its influences on calcium homeostasis, PTH exerts an opposing influence on serum phosphate. PTH secretion is STIMULATED by elevated serum phosphate. PTH directly reduces renal tubular reabsorption of phosphate from glomerular filtrate (phosphaturic effect). In interpreting what's happening clinically, it is important to realize that when the parathyroid gland is presented with conflicting signals from the serum phosphate and serum calcium, calcium wins!

**CAVEAT:** It is reasonable to expect a RECIPROCAL relationship between serum phosphate and serum calcium levels when PTH derangement is a primary disorder.

**Other Hormonal Players in the Calcium Homeostasis Game:**

**Vitamin D Group (calciferols):** In order of potency, calcitriol >> calcidiol > Vitamin D. The prominent influence of this group of steroid hormones is to promote gut absorption of BOTH calcium and phosphate, thus resulting in INCREASE in the serum level of both.

**Calcitonin:** A product of C-cells of the thyroid, calcitonin generally opposes PTH effect on bone, promoting uptake of calcium by bone; to a lesser extent, calcitonin promotes renal calcium excretion.
Thyroxine and triiodothyronine: the thyroid hormones regulate the pace of normal skeletal remodeling; in excess, net osteolysis can produce an increment in the serum calcium.

Estrogenic and androgenic steroids: Generally promote calcium and phosphate deposition in bone, increased bone formation, resorption of calcium from the urine, and reduced osteolysis.

And now……the clinical stuff!

Total serum calcium represents an equilibrium of protein-bound calcium and ionized calcium. Since only the ionized fraction produces signs and symptoms of disease, we need to estimate whether the protein binding of calcium is normal or abnormal. Practically speaking, this is done by looking at the serum albumin: for every 1 gram/dl decrement below the low-normal serum albumin concentration, serum calcium should be "corrected" by adding 0.8 mg/dl to the raw value. In the occasional case of very high albumin, you would need to subtract an equal value from the "raw" serum calcium. Since PTH is by far the dominant influence on serum calcium, we should approach hypercalcemia and hypocalcemia keeping the Cardinal Rule in mind:

- If serum calcium is HIGH, PTH should be low
- If serum calcium is LOW, PTH should be high

Thus, once hypercalcemia or hypocalcemia is confirmed, the "knee jerk" should be to measure PTH and assess its appropriateness or inappropriateness. If its response is inappropriate, a PTH disorder is to blame! Within this very important endocrine concept of “appropriateness”, remember that even a high-normal PTH may be inappropriate in the early stages of a disease causing high calcium, and a low-normal PTH may be inappropriate for a disease that is causing low calcium. In these settings, the PTH is no longer “doing the right thing”.

Hypercalcemia

Signs and Symptoms of Disease: since calcium is prominently involved in neuromuscular function and the action of striated and smooth muscle, the following signs and symptoms can affect patients who are found to be hypercalcemic:

- Fatigue/muscle weakness
- Depression
- Mental Status changes
- Coma
- Anorexia
- Nausea/vomiting
- Constipation
- Short QT interval on ECG

*Polyuria is a consequence of hypercalcemia's effect on renal water handling. Hypercalcemia induces a state of nephrogenic diabetes insipidus, meaning that the response of the kidney to vasopressin is impaired. As a consequence, insensible renal water loss due to the inability to concentrate the urine maximally, coupled with reduced oral intake due to nausea, vomiting, or anorexia, can lead to marked volume depletion. In turn, the volume depleted state results in reduced GFR and reduced net calcium excretion, with the net result of cascading hypercalcemia!
Differential Diagnosis: The Usual Suspects

Primary Hyperparathyroidism (PHP)

PHP is the most common form of hypercalcemia encountered in an ambulatory practice among patients who seem well. Thus, when a patient is incidentally found to have hypercalcemia on "lab-o-gram", you should be thinking about the case in terms of whether other findings are compatible with the diagnosis of PHP. The majority of patients with this disorder will be asymptomatic, and will have mild hypercalcemia (serum calcium < 12 mg/dl)--although severe disease and severe hypercalcemia do occur at times!

Clues to Diagnosis: If you know the actions of PTH, you will have the right search image!
- PTH increased (or "inappropriately normal")
- Urinary calcium normal or high (filtered load of calcium vastly increased in the setting of hypercalcemia, which usually means that even though PTH is stimulating avid reclamation of calcium from the urine, there is still net hypercalciuria)
- Calcitriol serum level normal or high
- Serum phosphate often low
- Serum chloride often high
- Serum alkaline phosphatase often high (reflects increased osteoblastic activity in the high skeletal turnover state induced by increased PTH activity)

Morbidity: Patients can experience problems related to any of the target organs impacted by PTH, or related to hypercalcemia itself, as listed above. Target organ problems can include:

Bone Disease:
- Subperiosteal bone reabsorption (best seen in plain hand X-rays)
- Cystic bone disease
- Osteoporosis
Renal Disease:
- Nephrolithiasis
- Nephrocalcinosis (can lead to renal failure)

Any of the above, plus symptomatic or severe hypercalcemia, represent indications for parathyroidectomy surgery.

Pathology and Associated Findings: Over 85% of the time, PHP is caused by a parathyroid adenoma. The majority of the remainder of cases is due to parathyroid hyperplasia involving all of the glands. Hyperplasia would be expected in the setting of a family history strong for hyperparathyroidism, and when the family history is positive, you should consider working the patient up for multiple endocrine neoplasia I (3 P's: Pituitary adenoma, pancreatic islet cell tumor, and parathyroid hyperplasia) and
IIA (pheochromocytoma, medullary thyroid carcinoma, and parathyroid hyperplasia). Rarely, PHP is due to a parathyroid carcinoma.

**Malignancy-related Hypercalcemia**

The expected clinical presentation of this form of hypercalcemia contrasts markedly with the usual case of primary hyperparathyroidism: patients with cancer-related hypercalcemia as a rule appear ill, have symptomatic hypercalcemia, and usually have a known or at least obvious malignancy (as opposed-to the fabled "occult" malignancy). Among hospital inpatients with hypercalcemia, this is statistically the most common etiology.

**Mechanisms of Hypercalcemia in Malignancy**

- Local osteolysis via bone metastases (example: breast cancer)
- Production of osteolytic cytokines by tumor cells (example: multiple myeloma)
- Unregulated conversion of calcidiol to calcitriol (example: T-cell lymphoma)
- Production of PTH-related peptide by tumor cells, mimicking the actions of PTH on bone and the kidney. Although there is substantial structural homology with PTH, PTHrP is immunologically distinct: and thus, serum PTH is low in patients with this form of hypercalcemia.

As a general rule, cancer-related hypercalcemia is more severe than hypercalcemia encountered in PHP. In part this is related to cancer related cachexia, poor oral intake, and the symbiotic effect of accelerated renal water loss and inadequate replacement of water loss via the enteral route.

**Clinical Features:**

- PTH low
- Serum Calcium high
- Serum phosphate low (except in calcitriol-mediated hypercalcemia; see below)
- Azotemia common (elevated BUN and creatinine)
- Urine calcium high
- Stigmata of advanced malignancy (usually)

**Hypercalcemia of Granulomatous Diseases**

The setup in this group of disorders is the identification of a granulomatous disorder. Sarcoidosis is the most common of these diseases, but fungal disease, TB, berylliosis, etc. can also be associated with this form of hypercalcemia. The mechanism of hypercalcemia is the unregulated hydroxylation of calcidiol to the far more potent calcitriol, which causes hyperabsorption of calcium and phosphate from the gut. In this form of hypercalcemia, PTH is appropriately suppressed by serum calcium concentration above set point. Consequently, with PTH "out of the game", the high filtered load of calcium produces disproportionately high urinary calcium. Low PTH also results in reduced urinary phosphate excretion, and thus serum phosphate tends to be high, in contrast with hyperparathyroidism. Glucocorticoids markedly reduce
calcitriol-mediated gut absorption of calcium and phosphate, and thus represent excellent therapy for this syndrome.

**Clinical Features:**
- PTH low
- Calcitriol high
- Serum phosphate high
- Urine calcium very high

**Vitamin D intoxication**
In greater than physiologic replacement doses, Vitamin D can act to enhance gut calcium and phosphate absorption. *The best clue to diagnosis is identification of prescription or over-the-counter use of Vitamin D-containing products.* Because PTH will be suppressed by the high serum calcium, calcitriol production is usually reduced. *The best test to confirm the diagnosis is the serum level of calcidiol (25-OHD),* since the hepatic hydroxylation step is unregulated and largely substrate-dependent. Steroid therapy is effective, but must be continued for several weeks in cases of severe intoxication, owing to the lipophilic nature of calcidiol and the resultant prolonged biological half-life.

**Clinical Features:**
- PTH low
- Serum phosphate high (or high-normal)
- Urine calcium high
- Serum calcidiol high
- Serum calcitriol normal or slightly high

**Familial Hypocalciuric Hypocalcemia (FHH)**
This is a rare disorder that has been found to be associated with an inactivating mutation in the gene for the calcium-sensing receptor. The calcium-sensing receptor is highly expressed in the parathyroid glands and the kidney. The mutation in FHH makes the receptor less sensitive to calcium. In the parathyroid glands, this defect means that a higher than normal serum calcium concentration is required to reduce PTH release. In the kidney, this defect leads to an increase in tubular calcium and magnesium reabsorption. The fractional excretion of calcium is less than 1 percent in patients with FHH, indicating that more than 99 percent of the filtered calcium has been reabsorbed despite the presence of hypercalcemia (Ca/Cr clearance ratio = [Urine Ca x serum Cr] ÷ [Serum Ca x Urine Cr]). The net effect is hypercalcemia, hypocalciuria, and frequently hypermagnesemia. FHH is inherited as an autosomal dominant trait with high penetrance. Affected heterozygous patients typically present in childhood with the incidental discovery of hypercalcemia and hypocalciuria. Adults are also found to have this disorder when incidentally found to have hypercalcemia on a chemistry profile. The fact that patients with FHH have few if any symptoms or signs of hypercalcemia (e.g., constipation, polyuria, renal insufficiency, or neuropsychiatric disease) suggests that the calcium-sensing receptor may play a contributory role in patients with other forms of
hypercalcemia. The patient and family should be assured that FHH is a benign inherited condition that does not require parathyroidectomy.

Clinical Features:

- PTH high-normal or slightly high
- Serum phosphate normal
- Urine calcium very low

### MAJOR CHANGES IN MOST COMMON CAUSES OF HYPERCALCEMIA

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<th>Calcium</th>
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### Miscellaneous Causes of Hypercalcemia

In general, these remaining causes of hypercalcemia produce mild, asymptomatic hypercalcemia, although there are exceptions. Mechanisms of hypercalcemia include increased skeletal turnover as seen in immobilization hypercalcemia, usually heralded by an increased serum alkaline phosphatase; gut hyperabsorption of calcium; and decreased GFR states resulting in increased renal tubular reabsorption of filtered calcium.
Lithium raises "set point" for PTH release; thus, effectively it is a reversible cause of PHP!

**Treatment of Hypercalcemia**

- Correct volume depletion and dehydration with fluid resuscitation
- Parathyroidectomy, if indicated
- Drug therapy:
  - Bisphosphonates (block osteolysis)--drug of choice for malignancy-related hypercalcemia
  - Calcitonin--short-lived efficacy; high dose required; rapid onset of action
  - Glucocorticoids--only effective in Vitamin D intoxication, granulomatous diseases, and hematologic malignancy-related hypercalcemia
- Treat the underlying disorder!

**Hypocalcemia**

The dominance of PTH in calcium homeostasis is also of major importance as we consider the differential diagnosis of hypocalcemia. As we established, if ionized serum calcium falls, PTH should be "turned on". Most of the time an elevated PTH and hypocalcemia occur together, there is renal insufficiency. Among the factors driving the elevated PTH and low calcium are a low level of conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and retention of phosphorus. This condition is called “secondary hyperparathyroidism” because the root cause of the problem is the renal disease. In this situation, the serum phosphorus is elevated once the renal function drops below about 20% of normal. From the viewpoint of calcium and phosphate balance, the hypersecretion of PTH is initially appropriate as renal function declines. By increasing calcium and phosphate release from bone and enhancing urinary phosphate excretion (via a decrease in proximal reabsorption), PTH can attempt to correct both the hypocalcemia and the hyperphosphatemia. The effect on renal phosphate handling is manifested by a progressive reduction in the fraction of the filtered phosphate that is reabsorbed, from the normal value of 80 to 95 percent to as low as 15 percent in advanced renal failure. Ultimately, the hypersecretion of PTH has deleterious consequences on bone causing increased skeletal turnover, manifest by accelerated subperiosteal bone reabsorption and occasionally cystic bone changes.

If calcium is low and PTH is not “turned on” due to a PTH deficiency (congenital or acquired) or there is impaired action of PTH, we can predict accurately what will happen based on the known actions of PTH. In such conditions, serum ionized and total calcium will of course be low. The absence of PTH effect on the kidney will result in increased urinary excretion of calcium relative to the serum calcium, and decreased urinary excretion of phosphate such that the serum phosphate will usually be high. The concurrent findings of serum hypocalcemia and hyperphosphatemia, in the setting of anything short of end-stage renal disease identifies a problem with either PTH production or PTH action.
Signs and Symptoms of Hypocalcemia

The signs and symptoms of hypocalcemia relate to impaired neuromuscular function, ranging from minor annoyance to life-threatening. Chvostek's sign is elicited by tapping over the facial nerve and observing involuntary contraction of the ipsilateral facial muscles (it's important to know that 10% or so of normocalcemic patients will have a positive Chvostek's!). Trousseau's sign is elicited by inflating a BP cuff above systolic pressure for about 2-3 minutes and observing a carpal spasm downstream. Symptoms of hypocalcemia are summarized as follows:

Sign and Symptoms of Hypocalcemia

- Acral and perioral paresthesias
- Carpopedal spasm (pseudotumor cerebri)
- Laryngospasm
- Seizure
- Mood disorder / irritability
- Increased intracranial pressure
- Prolonged QT interval
- Cardiac arrhythmias

Differential Diagnosis of Hypocalcemia

**PTH Absent** $\Rightarrow$ Hypoparathyroidism
- Acquired (postoperative)
- Congenital
- Autoimmune
- Hypomagnesemia

**PTH Action Impaired** $\Rightarrow$ PTH resistance
- Pseudohypoparathyroidism
- Hypomagnesemia

**Vitamin D Problems**
- **Deficiency**
  - Low dietary intake
  - Low sunlight exposure
  - Malabsorption
- **Impaired activation**
  - Severe liver disease (impaired 25-OH’ase)
  - End-stage renal disease (impaired 1-OH’ase)
- **Vitamin D resistance** (Vitamin D-dependent rickets, Types I and 11)

**PTH Effects Overwhelmed**
- Severe hyperphosphatemia
- Tumor lysis syndrome
- Rhabdomyolysis
- Acute renal failure
- Sepsis
- Acute pancreatitis

### Differentiating Hypocalcemic Disorders

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<th>Disorder</th>
<th>Serum Calcium</th>
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<td>Calcitriol low</td>
</tr>
</tbody>
</table>

### Postoperative Hypocalcemia

*The most common cause of postoperative hypocalcemia following neck exploration or thyroid surgery is transient or permanent hypoparathyroidism.* If the patient has had surgery for primary hyperparathyroidism, the differential obviously includes hypoparathyroidism, but there are other possibilities unique to this situation. Sometimes, patients develop hypomagnesemia; *magnesium is critically important to the normal production, release and action of PTH and if low, a functional hypoparathyroidism and impaired action of PTH is observed.* Correction of hypomagnesemia promptly restores normal PTH function. The other phenomenon which can occur following PHP surgery is *transient suppression of PTH release from the remaining normal parathyroid glands due to the longstanding hypercalcemia, plus avid uptake of calcium and phosphate by bone: the so-called "hungry bone" syndrome.* This phenomenon is usually encountered when the patient has had severe cystic or erosive bone disease, and *an important clue to diagnosis is the concurrent finding of hypophosphatemia and hypocalcemia.* Supplementation of both calcium and phosphate may be required, but this condition will ultimately resolve in a self-limited fashion.

### Treatment of Hypocalcemic Disorders

**Emergent Treatment of Symptomatic Hypocalcemia:** One ampule of calcium gluconate solution should be given intravenously, followed by the continuous infusion of 8-10 ampules of calcium gluconate in one liter of saline solution over 6-10 hours.

**Chronic Treatment:**

* Dietary calcium supplements of 2-3 grams elemental calcium, daily
* Vitamin D therapy: Synthetic calcitriol (Rocaltrol) 0.25-1 mcg orally, daily, in one or two doses
* Thiazide diuretics, with concurrent dietary sodium restriction, decreases renal calcium excretion
* Recombinant parathyroid hormone (teriparitide) can be used by it is not currently an FDA approved indication
Must carefully monitor serum and urinary calcium; remember that for any serum calcium level, patients with absent or ineffective PTH will have abnormally high urinary calcium. When the serum calcium is frankly high iatrogenically, these patients are at high risk for renal stone disease and renal failure due to nephrocalcinosis.

Returning to your first patient…..

A 19-year-old woman presents for an induction physical prior to Army basic training. She is asymptomatic and her physical examination is normal. Routine laboratory testing identifies a calcium level of 11.1, with no other abnormalities seen on a complete metabolic panel, complete blood count, or routine urinalysis.

What other questions should you ask?
First, ask about a personal history of nephrolithiasis, fatigue, bony pain, polyuria, nausea, vomiting, or constipation. Next, ask about a family history of nephrolithiasis, hypercalcemia, and symptoms that might suggest hypercalcemia. Her medical history and pertinent review of systems is completely negative, and she recalls some vague recollection that her mother has also had high calcium levels.

What additional laboratory testing should you obtain? What causes of her hypercalcemia should you consider?
The most useful tests are a serum PTH level (most important next step) and a urinary calcium level to facilitate the calculation of a fractional excretion of calcium. Her PTH level is in the upper level of the normal range, and her urinary calcium level is low enough that her fractional excretion is less than one. These findings are essentially diagnostic of familial hypocalciuric hypercalcemia. If she had hyperparathyroidism, she would have had an inappropriately high PTH level (upper half of normal or elevated) and normal or high urinary calcium in the setting of an elevated serum calcium—and her serum phosphate also would have been low, whereas it was normal in this case. With malignancy or granulomatous disease, you would expect her to be symptomatic, and the PTH level would be low (since the hypercalcemia is being driven by non-PTH means). You would not be wrong to order a chest x-ray to exclude malignancy or granulomatous disease, but with the available results, you already have a diagnosis and do not really need to order this.

Should she be allowed to enter the military?
Yes, this is an asymptomatic condition that should not interfere with her ability to perform in the military.
Returning to your second patient…..
A 23-year-old male presents after successfully completing basic training. He has abrupt-onset colicky right flank pain radiating to the groin and new gross hematuria on one occasion. He is otherwise healthy with a normal physical examination. Routine laboratory testing reveals a serum calcium of 11.5, a serum phosphorus of 5.0, with otherwise normal metabolic panel and complete blood count. Urinalysis confirms RBCs and blood without other abnormalities.

What other questions should you ask?
First, ask about a personal history of prior flank or groin pain, fatigue, bony pain, polyuria, nausea, vomiting, or constipation. Also ask about any over-the-counter supplements or medications that he has been taking recently. He denies any supplements or recent medications. Next, ask about a family history of nephrolithiasis, hypercalcemia, and symptoms that might suggest hypercalcemia. His medical history and pertinent review of systems is completely negative, but he recalls that his father has to take steroids for a lung condition and has also had “calcium problems” though he cannot define what they are.

What additional laboratory testing should you obtain? What causes of his hypercalcemia should you consider?
The most useful tests for this case are a serum PTH level and vitamin D levels. His PTH level is at the lower limit of the normal range, and his 25-OH vitamin D level is elevated. On further testing, 1,25-OH vitamin D is also high and 24hr urine collection of calcium is higher than expected for his weight. These findings (when lack of vitamin D intake is confirmed) are essentially diagnostic for vitamin D intoxication in the setting of granulomatous disease. If he had primary hyperparathyroidism, he would have had an inappropriately high PTH level (high-normal or elevated) with normal or high urinary calcium in the setting of an elevated serum calcium. His serum phosphorus would have been low, whereas it was high in this case. With malignancy, you would expect him to have some advanced manifestations to include weight loss, malaise, anorexia, lymphadenophathy, night sweats, etc., and the PTH level would also be low. Phosphorus levels would typically be normal in malignancy but could be slightly elevated in actively lytic bone lesions. You would be correct to order a chest x-ray to exclude malignancy vs. granulomatous disease, looking for mediastinal lymphadenopathy and lung lesions. Palpable lymphadenopathy or skin lesions would be diagnostic on biopsy. His ethnicity (African) and family history are clues to his true diagnosis. Sarcoidosis patients, like this one, tend to have milder presentations than those with malignancies. 4% of sarcoidosis patients will present with nephrolithiasis as their first manifestation of disease.

Should she be allowed to continue in the military?
Possibly. If a brief course of glucocorticoids puts him into prolonged remission, it is possible that he could stay on active duty. However, since both active steroid use and recurrent hypercalcemia are both non-deployable conditions, there is a high likelihood that he will be medically discharged from active duty service.
Practice questions (and answers)
1. A 70-year-old man presents to the Emergency Department with disorientation. You suspect a diagnosis of hypercalcemia secondary to malignancy. If you learn that his serum calcium is 16 mg/dL with a low serum phosphate this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely

2. A 82-year-old female presents for a routine follow-up appointment. She feels well and is found to have a mildly elevated serum calcium with a mildly decreased phosphate. If you were considering a diagnosis of primary hyperparathyroidism and you found that her PTH was in the high normal range, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely

3. A 65-year-old retired Army Colonel presents for evaluation of an incidental laboratory finding of a calcium of 11.1. If you were considering a diagnosis of primary hyperparathyroidism and you learned that her serum phosphate is 5.5 (elevated), this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely

4. A 65-year-old retired Army Colonel presents with confusion. Laboratory findings are notable for a calcium of 14.1. If you were considering a diagnosis of cancer induced hypercalcemia and you learned that her serum PTH is undetectable, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or much less likely
**Answers:**

1. a. Much more likely. The serum calcium is markedly elevated with a low phosphate in a symptomatic patient.

2. a. Much more likely. The PTH is inappropriately high given that the patient has an elevated serum calcium which supports a diagnosis of primary hyperparathyroidism. With an elevated serum calcium the PTH should be suppressed.

3. b. Much less likely. HPT causes a low phosphate through PTH effects. If the phosphate is high, consider other causes as it should be low or low normal in primary HPT (a useful heuristic)!

4. a. Much more likely. Cancer often induces hypercalcemia by PTH related peptide which is not detected as serum PTH so the PTH value is often undetectable in patients with hypercalcemia due to PTHrp.

**Diagnostic Algorithm: Hypercalcemia**

**Diagram**
Hypercalcemia/Hypocalcemia

A 47-year-old woman is referred to your clinic by her family physician because of a serum calcium concentration of 11.6 mg/dl (normal 8.5 – 10.4 mg/dl), which was unexpectedly discovered during a routine physical and laboratory examination for a new job.

**Question # 1:** List the three forms of calcium in serum. Which form (s) is (are) measured by the automated serum analyzer.

**Question # 2:** List the two hormones that control the serum calcium concentrated in the eucalcemic individual. Where does each of these hormones work?

**Questions # 3:** List at least 7 causes of hypercalcemia. Which cause (s) are most likely in this patient and why?

You review the patient’s chart and perform a complete history and physical examination and find that your patient has had a mildly elevated serum calcium for the last 4 years. She has been in excellent health except for one episode of flank pain associated with hematuria which resolved on its own. Her father had nephrolithiasis and hypertension. There is no family history of any endocrine disease. She takes no medications or nutritional supplements. Her physical examination is completely normal. She weighs 60 kg.
**Question #4:** List the laboratory and radiographic tests that you would obtain at this point in the workup of this patient's hypercalcemia. For each test, explain what the laboratory test will tell you and indicate whether the test helps to identify the cause versus the effect of the underlying clinical condition.

Despite your carefully planned out (and cost effective) laboratory evaluation, the following laboratory and radiologic test results were obtained:

Na - 138 mEq/l  
K - 4.1 Meq/l  
Cl - 106 Meq/l  
HC03 - 26 mEq/l  
Total Protein - 7.9 g/dl  
Albumin - 4.2 g/dl  
Alkaline Phosphatase - 141 u/l (normal: 36-125)  
Creatinine - 1.3 mg/dl  
Parathyroid hormone (PTH) 103 (Normal: 10-65)  
25 (OH) Vitamin D- normal  
1,25 (OH)2 Vitamin D- Slightly elevated  
Parathyroid hormone related protein (PTHrP) - Normal  
Vitamin A - normal  
Free T4 - 19.5 pmol/l (normal: 10.3 - 30.6)  
TSH - 2.30 uU/ml (normal: 0.51 - 4.90)  
Serum Protein Electrophoresis - Normal profile  
Urine Protein Electrophoresis - No protein spike  
24 hr Urine calcium - 350 mg/24 hours (normal < 4 mg/kg/d)  
24 hr Urine creatinine - 1.32 gm/d  
Total volume 1400 cc  
Chest X-ray - Normal  
KUB – Two radio-opacities in the left kidney, consistent with nephrolithiasis.

Forearm bone mineral density – low  
Spine bone mineral density – low normal  
Hip bone mineral density – normal  
Bone scan – No focal uptake
**Question #5:** What is the likely cause of your patient’s hypercalcemia? List at least four tests that support your impression, and explain why. Give at least one reason each for excluding your next three possible diagnoses. Explain your rationale.

**Question #6:** This patient is felt to have primary hyperparathyroidism. Given this diagnosis, list other medical conditions that you would consider that are associated with primary hyperparathyroidism.

Your patient undergoes a neck exploration. Two days after the operation, the patient complains of perioral numbness. On physical examination, Trousseau’s and Chvostek’s signs are present. An EKG on shows a prolonged QT interval on her admission. A serum calcium is 7.3 mg/dl, a serum albumin, 4.0 mg/dl, and a serum phosphate 6.0 mg/dl. A serum PTH measurement is pending.

**Question #7:** List at least six causes of hypocalcemia. What is (are) the most likely cause (s) for this patient’s hypocalcemia?

**Question #8:** Explain how to test for a Trousseau’s and Chvostek’s sign on physical examination. What defines a positive test and what does it mean clinically.
Unfortunately, your patient remains hypocalcemic permanently, and requires therapy with oral calcium and vitamin D. Six months later her serum calcium is 10.2 mg/dl.

**Question #9:** List two reasons why you should be concerned about your patient’s calcium level, even though it is within the normal range. How does the absence of PTH affect the way in which the kidney filters calcium?
Introduction to Clinical Reasoning:
Obstetric Issues
(Prenatal Care and Labor & Delivery)

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Prenatal Care

Introduction:
In providing initial prenatal care to obstetric patients, several questions should be
considered in addressing the current pregnancy and potential health risks for the mother
and fetus, such as:

1. What are your goals with her initial visit?
2. What prenatal screening should be performed during her pregnancy, and when?
3. What diseases in pregnancy may the patient be at risk for?
4. What significant past medical or surgical history is important relative to the
current pregnancy?

It is also important to not only remain cognizant of the initial conditions or risks
considered early in pregnancy, but to consider subsequent conditions or risks that may
develop during the pregnancy. Some questions to therefore consider include:

1. What additional health risks or conditions may affect the mother or fetus as the
pregnancy progresses?
2. How might these conditions affect monitoring during the pregnancy or timing of
delivery?
3. What are appropriate follow-up intervals, and how might these intervals change
depending on the development of additional conditions or complications?

Objectives:
At the end of this session, students will:
1. Understand the importance of preconception care
2. List the physiologic adaptations of pregnancy
3. Understand the need for and specifics of medical evaluations at prenatal visits
4. Understand common complaints in pregnancy and how to evaluate these
5. List common diseases in pregnancy and how to diagnose and differentiate these
   entities
Reference and Background Materials

The following section of the syllabus will provide the student with comprehensive information regarding pregnancy, prenatal care, and antenatal care.

Key Definitions and Acronyms:

Amniocentesis: Aspiration of amniotic fluid, usually transabdominally, for diagnostic or therapeutic purposes. (For example: to diagnose aneuploidies such as Trisomy 21 or to determine Fetal Lung Maturity).

Amniotic fluid: The fluid confined by the amnion.

Ante partum: Before labor or delivery.

Blood flow, uteroplacental: The circulation by which the fetus exchanges nutrients and waste products with the mother.

Chloasma (mask of pregnancy): Irregular brownish patches of various sizes that may appear on the face during pregnancy or during the use of oral contraceptives, secondary to elevated levels of estrogen and progesterone.

Chorionic villus sampling: The transcervical or transabdominal sampling of the chorionic villi for cytogenetic evaluation of the fetus. (Often used to diagnose aneuploidies.)

Contraception: Prevention of conception or pregnancy.

Cordocentesis (Percutaneous umbilical blood sampling, PUBS): A fetal assessment and therapeutic technique in which a needle is passed into an umbilical vessel and blood is sampled or treatment is given.

Corpus luteum: The cystic structure formed in the ovary at the site of a ruptured ovarian follicle. This produces progesterone which supports the pregnancy until the placenta has developed and taken over this role.

Culdocentesis: Needle aspiration of intraperitoneal fluid or blood through a puncture of the posterior vaginal fornix into the cul-de-sac.

Curettage: Scraping of the interior of a cavity or other surface with a curette.

Suction: Endometrial curettage using a suction catheter.
**Decidua:** Identifiable changes in the endometrium and other tissues in response to the hormonal effects of progesterone.

**D immunoglobulin [RhO(D) immunoglobulin]:** An immunoprotein that prevents D sensitization. Commercially it is known as RhoGAM®. Attaches to antibodies made when an Rh negative person has been exposed to Rh positive blood.

**Eclampsia:** The convulsive form of preeclampsia eclampsia syndrome. Tonic-clonic seizures.

**Ectopic pregnancy:** A pregnancy located outside the uterine cavity.

**Ectropion:** The growth of the columnar epithelium of the endocervix onto the ectocervix.

**Embryo:** The conceptus from the blastocyst stage to the end of the 8th week.

**Fetal Testing (non-stress testing):** Evaluation of the fetus by electronic fetal heart rate monitoring, when not in labor.

**Fetus:** The conceptus from 8 weeks until birth.

**Gonadotropin, Human chorionic (hCG):** A glycoprotein hormone that is produced by the syncytiotrophoblast and is immunologically similar to luteinizing hormone (LH).

**Gravida:** A pregnant woman.

**Gravidity:** The pregnant state, or the total number of pregnancies a woman has had, including the current pregnancy.

**Hydatidiform mole:** A pathologic condition of pregnancy characterized by the hydropic degeneration of the chorionic villi and variable degrees of trophoblastic proliferation.

**Intervillous space:** The space in the placenta in which maternal blood bathes chorionic villi, allowing the exchange of materials between the fetal and maternal circulations.

**Intrauterine fetal demise (IUFD, stillbirth):** Intrauterine death of a fetus. For purposes of vital statistics, a fetal death prior to 500 grams is usually classified as an abortus.

**Karyotype:** A photographic reproduction of the chromosomes of a cell in metaphase, arranged according to a standard classification.

**Labor:** The process of expulsion of the fetus from the uterus.

**Induced:** Labor that is initiated artificially.
**Stimulated (augmented):** Labor that is stimulated, usually with oxytocin. The labor is “assisted” after it has started on its own. (This is different from an Induction, in which labor has not started on its own.)

**Lactogen, human placental (hPL):** A polypeptide hormone that is produced by the syncytiotrophoblast, is similar to prolactin and somatotropin from the pituitary, and is involved in carbohydrate metabolism by the mother and fetus.

**LMP:** Last menstrual period. The LMP is the 1st day of the last menstrual period when used in reference to dating a pregnancy.

**LNMP:** Last normal menstrual period.

**Membranes, premature rupture of (PROM):** Rupture of the amniotic membranes before the onset of labor.

**Membranes, preterm premature rupture of (PPROM):** Rupture of the amniotic membranes before 37 weeks gestational age and before the onset of labor.

**Mosaicism:** The presence in an individual group of cells of different chromosomal constitutions.

**Multigravida:** A woman who is has delivered a fetus over 20 weeks gestation before.

**Parity:** The number of pregnancies delivered by a woman in which the fetus is over 20 weeks gestation prior to delivery.

**Placenta previa:** A condition in which the placenta is located in the lower portion of the uterus and covers part or all of the internal os.

**Preeclampsia:** A specific hypertensive disorder of pregnancy with the diagnosis made on the basis of hypertension with proteinuria. It usually occurs after the 20th week of pregnancy.

**Prematurity:** An infant born before 37 completed weeks (260 days) of pregnancy.

**Primigravida:** A woman who is pregnant for the first time.

**Quickening:** The first perception by the mother of fetal movement, usually between the 16th and 20th week of gestation.

**Sonography (ultrasonography, ultrasound):** In obstetrics and gynecology, a diagnostic aid in which high-frequency sound waves are used to image pelvic structures in pregnant and non-pregnant patients.

**Striae gravidarum:** Streaks or lines seen on the abdominal skin of a pregnant woman.
Supine hypotensive syndrome: A hypotensive syndrome often characterized by sweating, nausea and tachycardia. It occurs in some pregnant women in the supine position when the pregnant uterus obstructs venous return to the heart.

Trimester: A period of three months. The period of gestation is divided into three units of three calendar months each. Some important obstetric events may be conveniently categorized by trimesters.

Trophoblast: The epithelium of the chorion, including the covering of the placental villi. It comprises a cellular layer (cytotrophoblast) and syncytium (syncytiotrophoblast).

Tubercles, Montgomery: The enlarged sebaceous glands of the areolae of the mammary glands during late pregnancy and lactation.

NOB: New OB Clinic or appointment
ROB: Routine OB Clinic or appointment
COB: Complicated OB Clinic or appointment
APT: Antepartum Testing
NST: Non-stress test
AFI: Amniotic fluid index
BPP: Biophysical profile
PTL: Pre-term labor
HSV: Herpes
GBS: Group B (beta) streptococcus
CHORIO: Chorioamnionitis
SROM: Spontaneous rupture of membranes
AROM: Artificial rupture of membranes
PROM: Premature rupture of membranes
PPROM: Preterm premature rupture of membranes

Basic Science Highlights/Review:

General Physiology

Cardiac Physiology:
-plasma volume increases by 50%
-cardiac output increases 30-50% (4.5 to 6L/min)
-stroke volume increases about 10-15%
-pulse increase 15-20 bpm
-SEM and s3 gallop is common
-peripheral vascular resistance decreases
-BP decreases early in pregnancy
   -(5-10 mmHg systolic, 10-15 mmHg diastolic)
   -returns close to normal by third Trimester
-compensated respiratory alkalosis

Pulmonary Physiology:
-diminished pulmonary reserve
-arterial blood gas (ABG):
  - pH 7.44
  - pCO2 30
  - HCO3 20-25
  - pO2 100
-RR, vital capacity (VC), inspiratory reserve volume (IRV) unchanged
-functional residual capacity (FRC), expiratory reserve volume (ERV), residual volume (RV), total lung capacity (TLC) decreased
-inspiratory capacity, tidal volume (TV) increased

**Renal Physiology:**
-increase in kidney size and weight
-ureteral dilation (R>L)
-GFR Increases by 50%
-renal plasma flow Increases by 75%
-CrCl increases to 150-200cc/min
-BUN and serum Cr decrease by 20%
  - normal pregnant creatinine is less than or equal to 0.6
-increase in glucose excretion
  - glucosuria is often pregnant and can be a normal finding in pregnancy

**Hematologic Physiology:**
1. **Plasma Volume and RBC Mass:**
   - increase disproportionately:
     - Plasma Volume Increases 50%
     - RBC Volume Increases 25%
   - this results in a physiologic (dilutional) anemia of pregnancy
   - mean Hgb is 11.5 g/dL

2. **WBC and Platelets:**
   - WBC count increases
   - platelet count decreases

3. **Coagulation System**
   - hypercoagulable state
     - increased risk of blood clots such as DVT and PE
     - increased fibrinogen and Factors VII-X

**Gastrointestinal Physiology:**
-decreased motility – stomach empties slower, resulting in anesthetic risk with general endotracheal anesthesia.
-decreased tone of lower esophageal sphincter
  - resulting in increased prevalence of gastroesophageal reflux disease (GERD).
-reduced gastric acid secretion
Reproductive Physiology:
- Uterus:
  - weight increases from 70gm to 1100gm
  - blood flow increases to 750ml/min
  - 15% of cardiac output goes to uterus
- Cervix:
  - increase in water content and vascularity
  - increase in cervical mucus secretions

**Approach to Preconception Care**

**Approach:**

*Preconception care* is important, as it allows the provider to maximize the following:
- folic acid intake (to minimize neural tube defects)
- control of HTN
- control of DM
- control of thyroid disease
- control of other pre-existing diseases
- removal of teratogenic medications
- cessation of alcohol, tobacco, drugs
- update vaccinations
- familiarity with maternal diseases or exposures that are associated with classic fetal abnormalities

Nearly all organ systems are affected by pregnancy and change to adapt to the pregnancy. Your goal is to differentiate “normal” from “abnormal” complaints and findings.

**Prenatal Visits:**

Each prenatal visit differs based on the gestational age of a pregnancy. Early in pregnancy, visits are less frequent, as very few pregnancy-related problems occur between the 8th week of gestation and the 28th week of gestation. Laboratory values are obtained at various gestational ages.

**What are your goals with her initial visit?**

*Initial Visit:*

The initial obstetric prenatal visit aims to screen for any maternal diseases, abnormalities, history, or other issues that may indicate a difference in managing the pregnancy. For example, these scenarios require different clinical reasoning:

*If a patient has no medical or obstetric history, the visit may simply be an overall physical examination, initial laboratory data, and mainly focus on educating the patient about pregnancy and what to expect. This patient would likely not return for the next visit until 6 weeks later.*
Conversely, a patient with history of Cesarean delivery will require special consideration for delivery method with the current pregnancy. She may need an additional visit designed to focus on counseling and decision-making about delivery.

A patient who is 41 years old and pregnant is at increased risk for preeclampsia, gestational diabetes, fetal demise, and fetal chromosomal abnormalities. She may require more frequent visits.

What prenatal screening should be performed during her pregnancy, and when?

Prenatal Screening or Diagnosis:
Prenatal screening is a personal decision for each patient. Tests offered to each patient may differ depending on the medical history and current status of each patient. Deciding how to advise and counsel patients requires clinical reasoning.

There are several different ways to accomplish prenatal screening. Most commonly, maternal serum screening is performed, which can be done by a single second trimester serum test, the Quad Screen, or by first and second trimester serum testing. If first and second trimester testing is performed, the results can be used to predict risks for fetal abnormalities by either combining the results, an Integrated Screen, or be using the first trimester result to determine if second trimester screening is needed, a Sequential Screen.

Other ways to determine risk of fetal abnormalities include ultrasound evaluation and invasive testing. Ultrasound can be used in the first trimester to measure fetal nuchal translucency. In the second trimester, it can be used to evaluate fetal organs, looking for abnormal developments such as cardiac defects, foot abnormalities, cranial abnormalities and other development anomalies. Invasive testing can be accomplished in the first trimester by chorionic villi sampling and in the second trimester by amniocentesis.

For example, these scenarios would likely result in different methods of testing:

A 45 year-old G4P3003 presents at 5 weeks gestation having just discovered that she is pregnant. The pregnancy is unintended, and she is incredibly concerned about having a baby with a chromosomal abnormality. She plans to terminate the pregnancy if any abnormalities are identified. This patient is best served by offering an invasive diagnostic test such as chorionic villus sampling or amniocentesis to meet her needs.

A 24 year-old healthy woman presents for her first obstetric appointment. She is a primigravid patient, and inquires about noninvasive methods to screen for Down Syndrome, for which she realizes she is at an overall low risk. This patient is best served with either first trimester serum analytes with nuchal
translucency and/or second trimester quad screen and anatomic survey or sequential screening (first and second trimester serum screening) and anatomic survey.

What are diseases in pregnancy that she is at risk for?

**Preeclampsia** is a disease unique to pregnancy that involves hypertension and proteinuria. The treatment of cure is delivery. The management may differ depending on the gestational age and overall health of the mother. It is also important to differentiate preeclampsia from other diseases which are similar in presentation.

**Chronic hypertension** occurs before the 20th week of gestation, as compared with preeclampsia, which is more likely to occur in the third trimester. Chronic hypertension may or may not have associated proteinuria. Preeclampsia, by definition, always has associated proteinuria. Chronic hypertension is more likely to be associated with fetal growth restriction as a result of prolonged uteroplacental insufficiency.

**Gestational hypertension** is hypertension that is diagnosed after 20 weeks gestation but does not meet criteria for pre-eclampsia (i.e. less than 300mg of protein in the urine over 24 hours).

**Gestational diabetes** is very common in pregnancy. Typically, it develops by the end of the second trimester. Circulating glucose is preferentially shunted to the fetus, resulting in macrosomia and fetal hyperinsulinemia (the fetus’ response to high glucose exposure regularly). This can cause labor dystocia and delivery problems, as well as resultant neonatal hypoglycemia.

Gestational diabetes is impaired glucose tolerance, and is managed by optimizing postprandial glucose levels. The goal is to decrease the amount of chronic glucose exposure for the fetus. This is different than the management of chronic diabetes mellitus, which aims to optimize fasting and pre-prandial glucose values, designed to decrease long-term complications.

Clinical reasoning helps you to distinguish **pre-existing but undiagnosed diabetes mellitus** from gestational diabetes. Chronic diabetes, especially in the setting of poor control of glucose values, increases significantly the incidence of cardiac, renal, and vertebral abnormalities of a developing fetus. Women with chronic diabetes may have microvascular disease, resulting in growth restricted infants. This is in contrast to macrosomic infants of poorly controlled gestational diabetics. Patients with a prior macrosomic infant, previous gestational diabetics, who are overweight, or who have a family history of a fist-degree relative with diabetes should be screened early in pregnancy. Additionally, hemoglobin A1C
values can be helpful in distinguishing gestational diabetes from pre-existing diabetics when an early diagnosis is made.

**Preterm labor** is common in the United States without improvement over the last half-century. Preterm delivery presents a huge societal burden with costs of prolonged neonatal care and resultant chronic medical diseases or developmental problems in babies born prematurely.

**Preterm contractions** should be distinguished from preterm labor. Preterm contractions are contractions prior to 37 weeks gestation that do not lead to cervical dilation.

**Preterm** refers to gestational age, and is used to describe any pregnancy prior to 37 weeks gestation. **Premature** indicates a fetus that has not completed development, and is usually seen under 34-36 weeks gestation.

**Bleeding in Pregnancy:**

When evaluating bleeding in pregnancy, it is important to consider the gestational age.

**First trimester bleeding** results from spontaneous abortion, ectopic pregnancy, molar pregnancy, or can be normal gestation.

**Third trimester bleeding** may indicate placenta previa, abruption, or labor. **Placenta previa** is usually painless bleeding that classically occurs near the beginning of the third trimester. **Abruptions** usually cause pain or constant cramping and there is an associated risk factor such as hypertension, trauma, cocaine or tobacco use. An abruption is when the placenta separates from the uterus prior to the third stage of labor. **Labor** usually has more of a mucoid bloody discharge, and is associated with regular contractions and progressive change in the cervix.

**Pregnancy Loss:**

Pregnancy Loss **most commonly occurs in the first trimester**, and is seen in about 20% of all pregnancies. Clinical reasoning helps you differentiate between ectopic pregnancy, spontaneous abortion, and molar pregnancy, which all result in a loss and a grieving process for the patient.

**Spontaneous abortions** usually occur from nonrecurrent chromosomal abnormalities, and present with cramping, bleeding, and passage of tissue vaginally. **Ectopic pregnancies** result in pain and bleeding, but no passage of tissue. Ectopic pregnancies usually are diagnosed clinically with on the assistance of ultrasound evaluation. B-hCG levels do not increase at the normal rate. **Molar pregnancies** typically have markedly elevated B-hCG values and a cystic appearing mass is present in the uterus on ultrasound.
Second, and especially third, trimester losses are less likely to be chromosomal than first trimester losses. Although chromosomal abnormalities are possible, other etiologies such as umbilical cord accidents, infection, placental abruptions, maternal diseases, and maternal thrombophilias should be evaluated.

**Summary / Take Home Points:**

1. Preconception care is important and may change the management of a pregnancy.
2. Many physiologic adaptations take place in a normal pregnancy.
3. Medical evaluations differ at prenatal visits depending on the maternal health and gestational age.
4. Common diseases in pregnancy include preeclampsia, gestational diabetes, and preterm labor. These should be differentiated from similarly presenting diseases which may be managed differently, such as chronic hypertension, pre-existing diabetes, and preterm contractions.
Practice Questions/Answers:

1. Jennifer Gravidagain is a 23 year-old G4P2012 who presents to your clinic at 24 weeks gestation complaining of right sided flank pain. On exam, you elicit costovertebral angle tenderness. A renal ultrasound reveals a mildly dilated right ureter. What lab or physical finding would not help you to evaluate this patient to determine a potential diagnosis?
   A. Chest X-Ray
   B. Urinalysis and Culture
   C. CBC (Complete Blood Count)
   D. Temperature (Vital Signs)

2. Stephanie is a 16 year-old primigravid girl at 32 weeks gestation who complains of subjective dyspnea when walking up the stairs. What test results or findings would be consistent with a pulmonary embolism and not a normal decline in respiratory reserve?
   A. ABG (Arterial Blood Gas) with decrease in pO2 or increase in A-a gradient
   B. Normal respiratory rate
   C. Increase in Inspiratory Capacity
   D. Decrease in Total Lung Capacity

3. A 34 year old woman presents at 33 weeks gestation complaining of a headache, and swelling of her arms and legs. She is noted on evaluation to have a blood pressure of 155/98; repeat the blood pressure is 160/100. What is the most likely diagnosis?
   A. Gestational hypertension
   B. Viral upper respiratory infection
   C. Preeclampsia
   D. Migraine headache

4. A 24 year old woman at 9 weeks gestation presents with intermittent vaginal bleeding and occasional cramping. She has not been previously pregnant. What is the most appropriate next step in her evaluation?
   A. suction curettage
   B. transvaginal ultrasound
   C. pelvic exam
   D. serum quantitative human chorionic gonadotropin test
**Answers:**

1. A (Chest X-Ray): The differential diagnosis in this case is pyelonephritis versus nephrolithiasis, assuming an otherwise healthy young female. Urinalysis and Culture will determine if an infection is present (i.e. cystitis or pyelonephritis). Although nephrolithiasis will increase the risk of developing pyelonephritis, it does not usually present with an infection. The most chief complaint on presentation is pain. CBC will demonstrate an elevated white blood count (WBC) if an infection is present, but is typically not elevated with nephrolithiasis. Vital signs are important in narrowing down any differential diagnosis. If the patient has a fever, tachycardia, and hypotension, infection is very likely. With the development of hypotension, the patient may be developing shock or bacteremia, which can be life-threatening.

2. A (ABG) with decrease in pO2 or increase in A-a gradient: With a pulmonary embolism (PE), the ABG gives evidence of the thrombosis within the pulmonary vasculature by demonstrating a decrease in pO2 because less oxygen is being carried by the arteries due to a change in the exchange of CO2 and O2 in the lungs. This also gives a resultant increase in the A-a gradient. With a PE, the respiratory rate increases, whereas in normal pregnancy, there is not a change in respiratory rate. Normal pregnancy physiologic changes also cause an increase in Inspiratory Capacity and a decrease in Total Lung Capacity.

3. C (Preeclampsia): Although the differential diagnosis technically includes gestational hypertension, the markedly elevated blood pressures, combined with the headache, are very concerning for preeclampsia. Preeclampsia is defined by elevated blood pressure, and proteinuria; additional findings such as symptoms (headache, RUQ pain) and signs (such as elevated transaminases, fetal growth restriction, elevated creatinine) usually define a more severe degree of preeclampsia. Evaluation of this patient would include labs, fetal monitoring, and likely admission. If signs or symptoms designate the patient as severely preeclamptic, delivery is indicated, along with MgSO4 seizure prophylaxis.

4. C (Pelvic exam): The patient is presenting with a threatened abortion based on the cramping and bleeding in the first trimester. Approximately 25% - 50% of threatened abortions eventually result in loss of the pregnancy. The use of ultrasound is a very appropriate response; indeed the patient will require an ultrasound to evaluate for the presence of a fetus and to exclude ectopic pregnancy. However, the first aspect of evaluation is a pelvic exam, to look if the cervix is open and if there may be tissue in the cervical os (inevitable or incomplete abortion) as well as to evaluate the size of the uterus and for the presence of a pelvic mass.
Labor and Delivery

Introduction:
Evaluation of women presenting to the Labor and Delivery Suite involves several considerations, including:

1. What is the patient’s gestational age, and is she therefore presenting with premature rupture of membranes or preterm labor?
2. Are there any conditions during this pregnancy which make the labor and/or delivery process potentially complicated?
3. What are the three stages of labor, and which stage is the patient presenting in?
4. What are possible causes of labor dystocia should the labor process not progress according to normal labor curves depending on her parity?

Readings: The following reference provides an excellent resource regarding prenatal and antenatal obstetric care.


Objectives:
At the end of this session, students will be able to:
1. List common terminology used in obstetric care
2. Understand various fetal presentations and positions and methods to determine these.
3. List and define the stages of labor.
4. List common problems in labor and delivery and their management.

Reference and Background Materials

The following section of the syllabus will provide the student with comprehensive information regarding labor and delivery considerations.

Key Definitions and Acronyms: (NOTE: Some definitions and acronyms relative to this topic had been listed previously in the “Prenatal Care” section.)

Antepartum: Before labor or delivery.

Apgar score: A physical assessment of the newborn, performed at 1 and 5 minutes after birth, used to determine the need for resuscitation. Occasionally, a 10 minute Apgar score will be completed, as well.

Atony, uterine: Loss of uterine muscular tonicity, which may result in postpartum hemorrhage.
**Biophysical profile:** A physical assessment of the fetus, including ultrasound evaluation of gross fetal movement, breathing movements, fetal tone (flexion/extension of an extremity or hand), amniotic fluid volume and electronic fetal heart monitoring.

**Breech:** The buttocks (often refers to fetal presentation).

**Cesarean delivery:** Birth of the fetus through incisions made in the abdomen and uterine wall.

**Chorioamnionitis:** Inflammation and infection of the fetal membranes.

**Dilation:** The physiologic or instrumental opening of the cervix.

**“Double set-up”:** The simultaneous availability of two sterile set-ups for either a vaginal or abdominal delivery.

**Dystocia:** Abnormal or difficult labor.

**Effacement:** Thinning and shortening of the cervix.

**Episiotomy:** An incision made into the perineum at the time of vaginal delivery.

**Ferning:** The microscopic pattern of sodium chloride crystals as seen in estrogen stimulated cervical mucus or amniotic fluid.

**Hydramnios (polyhydramnios):** Excessive amounts (more than 2 liters) of amniotic fluid at term.

**Maturity:** The condition of a fetus weighing 2,500 grams or more.

**Mid pelvis:** An imaginary plane that passes through the pelvis and is defined by three points: the inferior margin of the symphysis pubis and the tips of the ischial spines on either side. This plane usually includes the smallest dimensions of the pelvis.

**Maternal Mortality:** Death of the mother.

**Fetal Mortality:** Death of the conceptus between >500 grams and birth.

**Stillbirth (intrauterine fetal demise):** Death of a fetus before birth.
For purposes of perinatal vital statistics, the fetus must be over 20 weeks gestational age or over 500 grams in weight.

**Neonatal:** Death of the infant in the first 28 days of life.

**Perinatal Mortality:** Death of the fetus or neonate between 20 weeks of gestation and 28 days after birth. It is the sum of stillbirths and neonatal deaths.
**Neonatal:** Referring to the first 28 days of life.

**Nonstress test (NST):** Evaluation of the fetus by electronic fetal heart monitoring, not in labor.

**Oxytocin:** An octapeptide formed in the hypothalamus and stored in the posterior lobe of the pituitary. It has stimulant effects on the smooth muscle of the uterus and the mammary glands. Pitocin is a synthetic form of oxytocin.

**Pelvic inlet:** An imaginary plane passing through the pelvis that represents the upper boundary of the true pelvis. It is bounded posteriorly by the promontory and alae of the sacrum, laterally by the linea terminalis, and anteriorly by the horizontal rami of the pubic bones and the upper margin of the symphysis pubis.

**Percutaneous Umbilical Blood Sampling (PUBS):** See cordocentesis.

**Perinatal:** Pertaining to the combination of fetal and neonatal periods, considered to begin after 20 weeks of gestation and to end 28 days after birth.

**Perineum:** The pelvic floor and associated structures occupying the pelvic outlet. The connective tissue between the vagina and anus.

**Polyhydramnios:** See hydramnios.

**Position:** The relationship of a designated point on the presenting part of the fetus to the maternal pelvis (example: left occiput anterior [LOA]).

**Postpartum:** After delivery or childbirth.

**Post-term pregnancy:** Pregnancy prolonged beyond the end of the 42nd week of gestation.

**Presentation:** The portion of the body of the fetus that is coming first in the birth canal. Examples include vertex, breech and shoulder presentations.

**Presenting part:** The portion of the fetus that is felt through the cervix on vaginal examination. The presenting part determines the presentation.

**Prolapse:**
- **Cord:** A condition in which the umbilical cord precedes the presenting part of the fetus.
- **Uterine:** Prolapse of the uterus, usually due to the loss of supporting structures. It is related to injuries of childbirth, advanced age or congenital weakness of connective tissues.
**Pseudocyesis:** False pregnancy, in which some of the signs and symptoms of pregnancy are present, although no conception has taken place.

**Puerperium:** The period after delivery in which the reproductive tract returns to its normal, nonpregnant condition, generally 6-8 weeks.

**Station:** The location of the fetal presenting part (leading bony point) relative to the level of the ischial spines. Station +2 means the presenting part is 2 cm below the ischial spines. Station -1 means the presenting part is 1 cm above the ischial spines.

**Vacuum extraction:** The use of a suction device placed on the infant’s head to assist vaginal delivery.

**VBAC:** Vaginal birth after cesarean delivery.

**Viability:** The condition of a fetus weighing 500 grams or more; the ability to live independently outside of the uterus.

L&D: Labor and Delivery
NST: non-stress test
AFI: amniotic fluid index
BPP: biophysical profile
PTL: pre-term labor
GBS: Group B (beta) streptococcus
CHORIO: Chorioamnionitis
SROM: Spontaneous rupture of membranes
AROM: Artificial rupture of membranes
PROM: Premature rupture of membranes
PPROM: Preterm premature rupture of membranes
FSE: fetal scalp electrode
IUPC: intrauterine pressure catheter
CLE: Continuous lumbar epidural
5/C/+2 the cervix is 5 centimeters dilated, completely effaced, and fetal part at +2 station

**Basic Science Highlights/Review:**

**Anatomy:**

The *blood supply of the uterus* comes predominantly from the uterine arteries. The uterine arteries arise from the anterior division of the internal iliac artery (also called the “hypogastric” artery). These arteries are accessed by entering the femoral artery and following its bath back to the common iliac artery. This route of access is useful in women with postpartum hemorrhage that has not responded to other means. An interventional radiologist may cannulate the femoral artery and guide a catheter into the uterine arteries to provide embolization.
The fetus must navigate through the pelvis to facilitate vaginal delivery using the cardinal movements of labor. The ischial spines indicate the level defined as “zero station”. The pubic symphysis may be “contracted”; in other words, the pubic rami may junction at an acute angle rather than an obtuse angle that we normally see. If this occurs, it may prevent delivery of the fetus. This abnormality is most frequently observed in an anthropoid pelvis. Other pelvic shapes include the gynecoid, platypoid, anthropoid, and android pelves.

Labor and vaginal delivery, in particular, involves significant stretching of pelvic tissue, including nerves that may result in pelvic floor neuroapathy. Pelvic floor musculature, including the levator ani and rectovaginal septum, may be injured during the labor and/or delivery process.

**Physiology and Pharmacology:**

*Uterotonics* work by creating more effective uterine contractions. Uterotonics may be used in managing acute postpartum hemorrhage from atony, but can also be used to augment or initiate contractions. Oxytocin is secreted from the pituitary gland and, its synthetic form used for labor and delivery, is known as “Pitocin”. Oxytocin receptors on the uterus increase in number toward the end of pregnancy. Oxytocin receptors are stimulated by either oxytocin or pitocin and the smooth muscle of the uterus then contracts. Pitocin/oxytocin are smooth muscle stimulators. These receptors can become saturated in cases of prolonged oxytocin exposure. Prostaglandins work by facilitating myometrial contraction at the cellular level. The student should review the side effects of oxytocin use, including risks and complications.

Oxytocin can cause tachysystole of the uterus, resulting in a prolonged severe contraction which can compromise or decrease the uteroplacental blood flow, thus decreasing oxygen delivery to the fetus. In this case, the fetal monitoring may show evidence of fetal distress.

**Fetal Presentation and Position**

**Fetal Lie vs. Presentation vs. Position:**

- *fetal lie* refers to the axis of the fetus in reference to the maternal axis
- *presentation* refers to the part of the fetus that is closest to the cervical os
- *position* refers to the rotation of the presenting part in reference to maternal anatomy

*A fetus with a breech presentation and a fetus with a cephalic presentation are both in a longitudinal lie.* If the sacrum of the breech fetus is toward the pubic symphysis of the mother, the fetus is said to have a sacrum anterior position. A cephalic fetus facing the maternal rectum at delivery is said to have an occiput anterior position.

**Breech Presentations:**
frank breech indicates a breech presentation with hips flexed, knees extended, and is the most common type of breech (Pike position)

complete breech indicates a breech presentation with hips flexed and both knees flexed as well (Similar to sitting “Indian Style”.)

incomplete breech indicates a breech presentation with at least one hip extended (“single footling” in the case of one hip extended, and “double footling” if both are extended)

Anterior vs. Posterior Fontanelle:

The anterior fontanel is bordered by the frontal and parietal bones. Due to the suture in the midline of the frontal bone, this fontanel is similar to a diamond shape on palpation

The posterior fontanel is bordered by the occipital bone and the parietal bones. Due to the smooth and non-sutured nature of the occipital bone, this fontanel is similar to a triangle shape on palpation, and is referred to as the lambdoid suture

Stages of Labor

False Labor vs. True Labor:

- In false labor, the cervix does not dilate, there are irregular contractions that are not progressive. Most women experience discomfort in lower abdomen that is relieved by sedation.

- In true labor, the cervix dilates and changes, there are contractions at regular intervals, the intervals progressively shorten, the intensity increases, and the pain is not relieved by sedation

First Stage:

- The first stage of labor includes both latent and active labor

- **Latent Labor** is slower and less predictable. Gradual cervical change occurs, including dilation, effacement, and consistency and position of the cervix. Usually, most women transition into active labor when the cervix is completely effaced and about 4 centimeters dilated.

- **Active Labor** is faster. Contractions are more regular and cervical change occurs at predictable rates (usually 1-2 centimeters hourly). This continues until the cervix is completely dilated, completely effaced, and no longer palpable in front of the fetal presenting part (i.e. the beginning of Stage 2).

Second Stage:

- The second stage of labor is defined as beginning upon complete dilation of the cervix, i.e. the cervix is no longer palpable in front of the fetus. This stage continues until delivery of the fetus is complete. A mother does not need to be actively pushing throughout this entire process, but “pushing” for delivery of the fetus is part of the second stage of labor.

Third Stage:
- The third stage of labor is defined as delivery of the placenta. The separation of the placenta is usually identified by a uterine contraction, increase in bleeding, and lengthening of the umbilical cord

**Fetal Monitoring During Labor**

Fetal monitoring can be accomplished continuously or intermittently. **External monitoring** includes a Doppler technology for assessing fetal heart rate, and an external pressure electrode, or tocometer, to assess the presence and relative strength of uterine contractions. The tocometer cannot provide a direct measurement in mmHg or cm H2O of uterine contraction strength.

**Internal monitoring** includes a direct electrical impulse assessment of fetal heart rate via the fetal scalp electrode. Internal measurement of actual intrauterine pressures can be assessed with an intrauterine pressure catheter, which compares the strength of uterine contractions to a column of water.

**Labor Complications**

**Labor Dysfunction:**
- **Protracted labor** means cervical change occurs (active phase) or fetal station advances (second stage), but at a slower rate than expected.
- **Arrested labor** means there is no change in the cervix (active phase) or fetal station (second stage). For arrest of labor to be considered, there has to be no change in either station or dilation over a minimum of 2 hours of labor with adequate contractions. An intrauterine pressure catheter (IUPC) can be used to assess adequacy of contraction strength (power). If there is no cervical change, labor is considered arrested. This is diagnosed as Arrest of Labor. If there is no change in station, this is diagnosed as Arrest of Descent.
- **Insufficient power** of labor can lead to protracted or arrested labor. The frequency and strength of contractions should be assessed. If suboptimal, augmentation with oxytocin or amniotomy may be helpful. This is the most common reason for protracted or arrested labor.
- The **passenger** can lead to dysfunction if there is a malpresentation or malposition, or if the fetus is too large. An assessment of the fetal presentation, position, and size should be performed. Malpositions may be corrected with manual rotations or forceps application.
- The **passageway** may lead to dysfunction. The shape of the pelvis may create a labor dystocia. The shape and size of the pelvis should be assessed.

**Infections in Labor:**
- **Chorioamnionitis** is a common infection during labor. The infection is rapid in onset, and associated with high fevers, uterine fundal tenderness, fetal tachycardia, and purulent malodorous amniotic fluid. The infection is usually polymicrobial and requires delivery for complete treatment.
Group B Streptococcus (GBS) colonization is not a maternal infection, but women who are colonized may pass the bacteria to the neonate, resulting in severe neonatal infections. To prevent this passage, GBS is treated during labor. Treating a patient prior to labor is not useful, as patients may become recolonized or the therapy may preferentially select for resistant bacterial strains.

**Delivery and Delivery Complications**

**Operative Deliveries:**
- **Operative vaginal deliveries** include forceps and vacuum assisted deliveries. Vacuums are associated with a greater risk of fetal subgaleal hemorrhage, while forceps are associated with a greater risk of maternal tissue trauma.
- **Cesarean deliveries** are performed by incising the abdomen and uterus to facilitate delivery of the fetus. Cesarean deliveries may be necessary when labor **arrests** despite adequate power, a nonreassuring fetal assessment (i.e. “fetal distress”) occurs and requires prompt delivery that cannot be accomplished vaginally, a **malpresentation** occurs (i.e. breech or shoulder presentation), severe **fetal macrosomia** exists (>5000 grams), a **fetal anatomic malformation** or deformation prevents delivery (i.e. large cystic hygroma or meningomyelocele) or a woman has a **medical contraindication** to vaginal delivery (i.e. Ulcerative colitis flare with risk for rectovaginal fistulae formation).

**Postpartum Hemorrhage**
- **Postpartum hemorrhage** is most commonly caused by uterine atony, which prevents an effective enough contraction of the uterus to result in compression of the spiral arteries. Postpartum uterine atony is most effectively prevented with uterine bimanual massage and prophylactic oxytocin. If atony occurs, it can also be treated with these measures in addition to uterotonics such as methylergonovine and prostaglandins. In some circumstances, control of hemorrhage may require uterine packing (guaze or a Bakri Balloon®), uterine artery embolization, laparotomy with B-Lynch sutures, or hysterectomy.
- Other causes of postpartum hemorrhage include lacerations of the pelvic floor and/or cervix, retained placental tissue, or coagulation abnormalities.

**Summary / Take Home Points**

1. There are **three stages** of labor:
   - In the first stage, the cervix completely dilates and effaces until it is no longer palpable
   - In the second stage, delivery of the infant occurs
   - In the third stage, delivery of the placenta occurs
2. The **cardinal movements** of labor occur to facilitate navigation of the fetus through the pelvis and birth canal.
3. **Labor dystocia** may occur because of lack of uterine contraction strength (“power”), an abnormal “passenger” (malpresentation, fetal anomaly), or an abnormal “passageway” (contracted pelvis).
4. Postpartum hemorrhage is most commonly caused by *uterine atony*. 
Practice Questions/Answers

1. Which of the following is NOT a cause of postpartum hemorrhage?
   A. Atony
   B. Vaginal laceration
   C. Placenta Previa
   D. Retained placenta

2. What is the definition of cervical effacement?
   A. Thinning of the cervix.
   B. Opening of the cervix.
   C. Movement of the cervix to an anterior position.
   D. Softening of the cervix.

3. A patient at term is progressing through labor slowly. Her membranes ruptured 3 hours ago, and she has been dilated to 5 cm for the last 3 hours. The estimated fetal weight is 3000 grams, and her pelvis is felt to be adequate. Her contractions are occurring at about two contractions per 10 minute period. What is the most appropriate intervention?
   A. Cesarean section
   B. Oxytocin infusion
   C. Discharge home and readmission when contractions increase
   D. Misoprostol for cervical ripening

4. A 33 year old woman, at 41 weeks gestation, was diagnosed with gestational diabetes during the current pregnancy. The estimated fetal weight was 4300 grams. She progressed through the first and second stages of labor with delivery of the fetal head, but the provider is experiencing significant difficult in delivering the remainder of the neonate. What is the most appropriate initial approach to correct this situation?
   A. replacement of the fetal head and proceeding with Cesarean section
   B. Suprapubic pressure
   C. Rotation of the fetus via pressure on the shoulder
   D. clavicle fracture
**Answers:**

1. C (Placenta previa): This is a cause of bleeding during pregnancy, but does not contribute to postpartum hemorrhage. While it can lead to an increased risk of placenta accreta, where the placenta grows into the uterine wall, it does not cause postpartum hemorrhage itself. Atony, vaginal lacerations, cervical lacerations, and retained placenta are all causes of postpartum hemorrhage.

2. A (Thinning of the cervix): Thinning of the cervix is effacement. Dilation is opening of the cervix. Movement to an anterior position and softening of the cervix are necessary cervical changes to allow the progression and development of active labor.

3. B (Oxytocin infusion): The patient’s contraction pattern is inadequate based on the frequency of contractions with no cervical change. It is important to assess adequacy of the pelvis as well as estimated fetal weight to assess for any potential dystocia relative to the size of the fetus relative to the shape and size of the maternal pelvis. Oxytocin infusion is used to augment contractions. Cesarean section may be indicated at some point if the labor still does not progress appropriately, but not at this point. Misoprostol is commonly used to induce labor, but is not appropriate to use once a patient is contracting on a regular basis.

4. B (Suprapubic pressure): This scenario is as classic description of shoulder dystocia. It is important to note that although gestational diabetes and macrosomia are associated with shoulder dystocia, most shoulder dystocia cases occur in the absence of either of these factors. The most important initial approach is to provide suprapubic pressure, usually along with sharp flexion of the maternal thighs (McRoberts’ maneuver). Additional steps, such as rotation or delivery of the posterior arm and shoulder, may be used if initial steps do not reduce the “stuck” shoulder. Emergent procedures, such as clavicular fracture, or possible replacing the fetal head and performing a Cesarean section (Zavanelli maneuver) may be indicated if all the other measures fail.
ASSIGNED READING:
Chapters 7 and 14

CHIEF COMPLAINT: “I don't feel well”

HISTORY OF PRESENT ILLNESS:

Petty Officer Sarah Childs is a 21 year-old G2P0010 Caucasian unmarried Navy E-4 Electronic Technician who was reassigned to the Washington, DC area one month ago from shipboard duty due to her pregnancy status. She is sure of her last menstrual period, which began 38 weeks ago. She presents today for the first time since her move. She has been seen by a provider four times during her pregnancy thus far: for an initial prenatal visit at 10 weeks gestation, and for follow-up appointments at 18, 25, and 30 weeks gestation. Her chart is available for review.

She experienced some mild nausea and vomiting which resolved around 13 weeks. Since that time, she has felt well until last night when she began experiencing right sided abdominal pain and a headache. She has also noted some increased edema. Her baby is moving well, and she denies regular contraction, vaginal bleeding, nor leakage of fluid from the vagina.

She is somewhat annoyed about the Navy reassigning her, as she is concerned this will impact her career negatively. Otherwise, she is happy with her new office assignment.

PAST MEDICAL HISTORY:
-Mild allergic rhinitis
-Simple cystitis - 2 episodes in last year
-She smokes cigarettes and has decreased to ½ pack per day

CURRENT MEDICATIONS:
-Prenatal vitamin

LAB DATA FROM OBSTETRIC CHART:
-CBC: Hgb 10.6gm, HCT 31%
-Urinalysis: trace protein, no glucose or blood.
-Blood type A+
-Antibody Screen: negative
-RPR: Nonreactive
-Rubella: Nonimmune
-Cervical Cytology: Normal
PHYSICAL EXAMINATION:
-BP: 146/94, P: 90, R: 18, T: 98.8
-Ht: 5'5, Wt: 156 lbs.

-Patient appears fatigued and mildly ill.
-Cardiac and lung exams are normal.
-Obstetric exam reveals a uterine fundal height of approx. 34 cm. Fetal heart tones are present by Doppler at 150 bpm.
-There is no calf tenderness, but significant 2+ pitting edema is apparent on bilateral lower extremities to the mid-calf. Her DTRs are brisk, 3+, but symmetric.
-A urinalysis is performed and reveals 2+ protein, negative for nitrite, LE, and bacteria. There are no WBCs or RBCs.

SOME OF THE QUESTIONS TO BE CONSIDERED AS YOU PREPARE FOR THE MANAGEMENT OF THIS PATIENT INCLUDE:

1. What issues need to be addressed now?
2. What are the essential components of today's visit?
3. Are there special concerns?
4. What is her differential diagnosis?
5. How would you further evaluate this patient?
6. How would you manage this patient?
7. Would you manage this patient differently if she were 28 weeks gestation?
8. Would you manage this patient differently if she had a creatinine of 1.5mg/dL?
9. What is her estimated date of confinement (EDC)? How is this determined?
   - What tests or signs can confirm or dispute the dating?
10. Discuss her social risk factors and how to address these.
11. What tests would you obtain on this patient today?
12. How would you treat this patient?
13. What tests or assessments are indicated at the initial visit of a pregnant woman?
   - Current visit? 28-32 weeks? 35-37 weeks?
CHIEF COMPLAINT:  "I started to have vaginal bleeding two hours ago."

HISTORY OF PRESENT ILLNESS:

LCDR Jones is a 34 year old Gravida 2, Para 1001, PHS nurse assigned to the Pine Ridge Indian Health Service Hospital in South Dakota. She is now 35 weeks gestational age and gives a history of a sudden onset of moderately heavy vaginal bleeding beginning 2 hours ago, soaking her underwear and one towel. She doesn't think her "water broke". She states that she has had mild intermittent lower abdominal cramps occurring about once every hour for the past week but denies experiencing any pain. The fetus has continued to have active movements. Review of the prenatal record reveals the following: Serial blood pressures since the 3rd month of gestation were in the 120-130/80-86 mm Hg range; 23 lb. total weight gain; Type O, Rh Positive blood with a negative antibody screen, Hct 36, Hgb 12; urinalysis negative; RPR non-reactive.; Pap is within normal limits (WNL) and vaginal/rectal swab is positive for Group B Strep. At 28 weeks her glucose screen was 150 mg/dl and Hct 34.5, Hgb 11.6. Her prenatal course was otherwise unremarkable.

PAST HISTORY:

- The term spontaneous vaginal delivery 4 years ago was complicated by gestational hypertension.
- She has had borderline hypertension since then but has not required medication.

REVIEW OF SYSTEMS:

- Urinary frequency throughout this pregnancy.
- She denies edema, weakness, syncope or headaches.

PHYSICAL EXAMINATION:

BP : 130/84, P : 80, R : 16, T : 37°
Ht: 5'5", Wt: 160 lbs.

- The patient appeared comfortable and in no acute distress.
- Abdominal examination revealed that the uterine fundus measured 35 cm above the symphysis pubis and the fetus was in an unengaged cephalic presentation. The uterus and abdominal wall were not tender. During the abdominal examination a uterine
contraction was felt which lasted 20 seconds, was moderate in intensity, and was followed by good relaxation.
- The fetal heart rate was reactive on external electronic monitoring, with a baseline heart rate of 140 beats per minute.
- Peripheral pulses and skin color were normal.
- Pelvic speculum examination revealed 10 cc of thin watery blood in the vaginal vault.
- The cervix appeared to be 80% effaced and 2 cm dilated.
- The bimanual vaginal and rectal examinations were deferred, pending further consideration of her most appropriate management plan.

PRELIMINARY LABORATORY DATA:
- Hct - 34%, Hgb 10.9
- WBC - 9,000; Differential - WNL
- Platelets - 350,000/cc
- Urinalysis - WNL

SOME QUESTIONS TO BE CONSIDERED AS YOU PREPARE TO MANAGE THIS PATIENT INCLUDE:

1. What are the most common causes for vaginal bleeding in the third trimester of pregnancy and how can they be distinguished clinically?
2. Would the presence or absence of labor, or of abdominal pain, be helpful in establishing a diagnosis? If so, how?
3. What is bloody show?
4. How is the diagnosis of labor made?
5. What additional information or tests would you order in this case?
6. Why was the bimanual examination of the pelvis deferred? Should the speculum examination of the vagina have been performed?
7. If the fetus were to be delivered now, how much would it probably weigh and how good (or poor) an outcome would it likely have? At what level facility should such a delivery occur?
Introduction to Clinical Reasoning:  
Gynecologic Issues

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General Gynecology

Introduction:
General gynecology involves primary care and well-women care including well woman care and screening for cervical, breast and colon cancer. Issues commonly encountered include menstrual irregularities, pelvic pain, sexual dysfunction and pelvic floor support disorders which commonly present as urinary and fecal incontinence. Some questions to consider include:

1. What medical and/or surgical conditions does your patient have or has had that could affect her gynecologic health?
2. What are the patient’s current screening needs?
3. What medications or nutritional supplements does your patient take?
4. Does the patient have any concerns regarding sexual health?
5. Does the patient have any symptoms relating to vaginal discharge, pelvic pain, pelvic pressure, or urinary/fecal incontinence? (Questions relating to menstruation will be addressed later in this case.)

Readings: The following reference provides an excellent resource regarding women’s health and gynecologic care.


Objectives:
By the end of this session, students will be able to:
1) Describe how to diagnose and manage common inflammatory condition such as vaginitis.
2) List types of female contraceptive methods, efficacy of various methods, and summarize available means of emergency contraception.
3) Summarize normal pelvic support and the defect that lead to pelvic organ prolapse, urinary and fecal incontinence and summarize the clinical evaluation and treatment approaches for these symptomatic defects.
4) Describe the pathogenesis, symptomatology, evaluation, and treatment options for endometriosis.
5) Describe common etiologies for infertility and initial evaluation and therapeutic options.
6) Summarize common benign and malignant neoplasms of the ovary and describe the evaluation of women with a pelvic mass.

**Reference and Background Materials**

The following section of the syllabus will provide the student with comprehensive information regarding well-women’s health and general gynecologic conditions.

**Key Definitions and Acronyms:**

**Adenomyosis:** Presence of endometrial tissue within the myometrial layer of uterus.

**Adnexae:** The uterine appendages, including the fallopian tubes, ovaries and associated ligaments.

**Adrenarche:** Development of pubertal hair growth patterns.

**Amenorrhea:** Absence or cessation of menstruation.

  **Primary:** Failure of menarche to occur by the 16th year of life.

  **Secondary:** Absence of menses for three or more months after menarche.

**Anovulatory bleeding:** Irregular uterine bleeding that occurs in the absence of ovulation.

**Bartholin cyst:** Cystic swelling of a Bartholin gland caused by obstruction of its duct.

**Bartholin glands:** A pair of glands located at the 4 o’clock and 8 o’clock positions on the vulvovaginal rim.

**Basal body temperature (BBT):** The oral temperature at rest, measured in the morning, used for detection of ovulation. The BBT will increase with ovulation.

**Benign cystic teratoma:** The most common germ cell tumor, consisting of matures elements of all three germ layers – ectoderm, mesoderm, and endoderm (often called dermoid cyst).

**Biphasic temperature curve:** A graph showing a basal body temperature in the luteal phase that is 0.3-1 degree F higher than that of the follicular phase, which indicates that ovulation has occurred.

**Breakthrough bleeding:** Endometrial bleeding that occurs at inappropriate times during the use of hormonal contraceptives. (i.e.) occurring at times other than during placebo pills.

**Cancer staging:** The clinical and pathological evaluation of the extent and severity of cancer.
Carcinoma in situ: A neoplasm in which the tumor cells are confined by the basement membrane of the epithelium of origin.

Climacteric: The period of life or the syndrome of endocrine, somatic and psychic changes that occurs in a woman during the transition from the reproductive to the nonreproductive state.

Clomiphene: A synthetic nonsteroidal compound that stimulates the maturation of ovarian follicles and thereby ovulation as a result of its antiestrogenic effect on the hypothalamus.

Coitus interruptus: Withdrawal of the penis during coitus before ejaculation.

Colporrhaphy:

   Anterior: A surgical procedure used to repair cystocele.

   Posterior: A surgical procedure used to repair rectocele.

Colposcopy: Examination of the vagina and cervix by means of an instrument that provides low magnification. This is used for the visualization of cellular changes that cannot be seen with the naked eye.

Condyloma acuminatum: A benign, cauliflower-like growth on the genitalia, thought to be caused by human papillomavirus.

Cone biopsy: A cone of cervical tissue excised for histologic examination.

Contraception: Prevention of conception or pregnancy.

Corpus luteum: The cystic structure formed in the ovary at the site of a ruptured ovarian follicle. This produces progesterone which supports the pregnancy until the placenta is developed and assumes the role of progesterone production.

Cul-de-sac: The pouch-like cavity (also called the Pouch of Douglas) between the rectum and the uterus, formed by a fold of peritoneum.

Curettage: Scraping of the interior of a cavity or other surface with a curette.

   Fractional: Separate curettage of the endometrium and the endocervix for diagnostic evaluation. Specimens are submitted separately for pathologic examination. The endocervical portion of the curettage is done first so as to avoid contamination of the sample with endometrial tissue.

   Suction: Endometrial curettage using a suction catheter. This is most commonly performed in the management of spontaneous abortion or in early pregnancy termination.

Cystocele: Protrusion of the urinary bladder that creates a downward bulging of the anterior vaginal wall as a result of weakening of the pubocervical fascia.
Cystometry: Measurement of the function and capacity of the urinary bladder by pressure-volume studies, often used to diagnose detrusor instability or stress urinary incontinence.

Cystoscopy: Direct endoscopic (visualization with a camera) inspection of the interior of the urinary bladder.

Dermoid cyst: See Benign cystic teratoma.

Dysgerminoma: A malignant solid germ cell tumor of the ovary.

Dysmenorrhea: Painful menstruation, usually characterized by cramping.

Dyspareunia: Difficult or painful intercourse.

Dysuria: Painful urination.

Ectropion: The growth of the columnar epithelium of the endocervix onto the ectocervix.

Endometriosis: The presence of endometrial implants outside the uterus.

Endoscopy: Instrumental visualization of the interior of a hollow viscus with a camera.

Enterocoele: A herniation of the small intestine into the cul-de-sac, usually accompanied by (and sometimes confused with) rectocele.

Estrogen replacement: The exogenous administration of estrogen or estrogenic substances to overcome a deficiency or absence of the natural hormone.

Eversion: See Ectropion.

Exenteration, pelvic: The removal of all pelvic viscera, including the urinary bladder, the rectum or both, usually in the setting of advanced cervical malignancy.

Fibrocystic changes (breast): Mammary changes characterized by fibrosis and formation of cysts in the fibrous stroma.

Functional ovarian cyst: A physiologic cyst arising from the Graafian follicle or the corpus luteum.

Functioning ovarian tumor: A hormone-producing ovarian neoplasm.

Gender (sex) role: An individual’s understanding and feeling of the activity and behavior appropriate to the male or female sex.

Gonadal agenesis: The congenital absence of ovarian (or testicular) tissue or its presence only as a rudimentary streak.

Gonadal dysgenesis: The congenitally defective development of the gonads.
**Gonadotropin:**

**Human chorionic (hCG):** A glycoprotein hormone that is produced by the syncytiotrophoblast and is immunologically similar to luteinizing hormone (LH).

**Human menopausal (hMG):** A preparation isolated from the urine of postmenopausal women, consisting primarily of follicle-stimulating hormone (FSH) with variable amounts of LH, used for ovulation induction.

**Pituitary:** An endocrine organ composed of the anterior gonadotropin secreting component and the posterior oxytocin secreting component.

**Granulosa cell tumor:** An estrogen-producing stromal tumor of the ovary that develops from granulosa cells and leads to premature feminization and/or hyperplasia and dysplasia of the endometrium.

**Hirsutism:** The development of various degrees of hair growth of male type and distribution in a woman.

**Hormone Replacement Therapy (HRT):** Estrogen and progestin replacement therapy.

**Hot flushes (flashes):** A vasomotor symptom characterized by transient hot sensations that involve chiefly the upper part of the thorax, neck and head, frequently followed by sweats, and associated with cessation or diminution in the ovarian secretion of estrogen.

**Hyperplasia, endometrial:** The abnormal proliferation of the endometrium with a marked increase in the number of glands or cystic dilation of glands. These changes may be related to prolonged unopposed estrogen stimulation. Hyperplasia associated with atypia (nuclear atypia) is associated with a higher risk of endometrial carcinoma.

**Hypoestrogenism:** A condition of subnormal estrogen production with resultant atrophy or failure of development of estrogen-dependent tissues.

**Hypogonadism:** The subnormal production of hormones by the gonads.

**Hysterectomy:**

**Abdominal (TAH):** The removal of the uterine corpus and cervix through an incision made in the abdominal wall.

**Radical:** The removal of the uterine corpus, cervix and parametrium, with dissection of the ureters; usually combined with pelvic lymphadenectomy.

**Laparoscopic Assisted Vaginal Hysterectomy (LAVH):** The combination of laparoscopy with vaginal surgery techniques to remove the uterus, cervix, and, frequently, the adnexa.
Robotic Assisted Laparoscopic Hysterectomy (RALH): The removal of the uterine corpus and cervix using computer and robotic controlled laparoscopic instruments via a surgeon controlled remote console.

**Subtotal (supracervical):** The removal of the uterine corpus, leaving the cervix in situ.

**Total:** The removal of the uterine corpus and cervix (without regard to tubes or ovaries).

**Vaginal (TVH):** The removal of the uterus and cervix through the vagina.

**Total Laparoscopic Hysterectomy:** The entire hysterectomy is performed via laparoscopy. The uterus may be removed either vaginally (via colpotomy) or morcellized and removed with a laparoscopic instrument. The vaginal cuff may be closed laparoscopically or vaginally.

**Hysterosalpingography:** Roentgenography of the uterus and tubes after injection of radiopaque contrast medium through the cervix. It is useful in ascertaining irregularities of the uterine cavity and patency of the fallopian tubes.

**Hysteroscopy:** The transcervical endoscopic visualization of the endometrial cavity.

**Hysterotomy:** Surgical incision of the wall of the uterus. This can be a transverse or vertical incision.

**Imperforate hymen:** Failure of a lumen to develop at a point where the budding vagina arises from the urogenital sinus. Although the hymen may not be broken down at all, patients often still have a vagina.

**Impotence:** The inability to achieve or sustain penile erection.

**Infertility:** The inability to achieve pregnancy with regular intercourse and no contraception within a stipulated period of time, often considered to be 1 year.

**Intraductal papilloma:** A benign mammary tumor, often multiple, occurring predominantly in parous women at or shortly before menopause. It is typically located beneath the areola and is often associated with bleeding from the nipple.

**Intrauterine device (IUD):** A device inserted into the uterine cavity for contraception.

**Intromission:** Introduction of the penis into the vagina.

**Laparoscopy:** The transabdominal endoscopic examination of the peritoneal cavity and its contents after inducing pneumoperitoneum.

**Leiomyoma (fibroid):** A benign tumor derived from smooth muscle that has a swirled appearance on microscopy.

**Leiomyosarcoma:** An uncommon malignant tumor of smooth muscle.

**Leukoaplaia:** An imprecise clinical term usually referring to white lesions of the vulva.
**Levator Ani Muscle:** The muscular sheet, consisting of the iliococcygeus, pubococcygeus and puborectalis muscles, which forms most of the pelvic floor (pelvic diaphragm) and supports the pelvic viscera.

**Libido:** Sexual desire or urge.

**Ligament:** Connective tissue attaching two anatomic entities.

- **Cardinal:** The dense connective tissue that represents the union of the base of the broad ligament to the supra vaginal portion of the cervix and laterally to the sides of the pelvis. It is considered to be the primary support of the uterus.

- **Uterosacral:** The peritoneal folds containing connective tissue, autonomic nerves and involuntary muscle arising on each side of the posterior wall of the uterus at about the level of the internal cervical os and passing backward toward the rectum, around which they extend to their insertion on the sacral wall. It is considered to play an important part in axial support of the uterus.

**Ligation, tubal:** The surgical or mechanical interruption of the continuity of the fallopian tubes for the purpose of permanent contraception.

**LMP:** Last menstrual period. The LMP is the 1st day of the last menstrual period when used in reference to dating a pregnancy.

**LNMP:** Last normal menstrual period.

**Masturbation:** Sexual stimulation by the manipulation of the genitals by oneself.

**Maturation index:** The ratio of parabasal to intermediate to superficial vaginal epithelial cells (e.g. 0/20/80), which is an indication of estrogen effect.

**Menarche:** The onset of menses.

**Menopause:** The permanent cessation of menses caused by ovarian failure or removal of the ovaries. Physiologic (not surgical) menopause is cessation of menses for 12 continuous months.

**Menorrhagia:** Excessive or prolonged uterine bleeding occurring at regular intervals.

**Metaplasia:** A reversible change in which one adult cell type is replaced by another cell type. The most common type of epithelial metaplasia is the replacement of columnar cells by stratified epithelium (squamous metaplasia).

**Metrorrhagia:** Uterine bleeding occurring at times other than the expected menses; for example, intermenstrual bleeding.

**Mosaicism:** The presence in an individual group of cells of different chromosomal constitutions.

**Mucus, cervical:** The secretion of the cervical mucous glands; its quality and quantity are influenced by estrogen and progesterone. Estrogen makes it abundant and clear (which is called spinnbarkeit) with a fern pattern on drying. Progesterone makes it scant, opaque and cellular without a fern pattern upon microscopic examination. The cervical
Mucus characteristics will change relative to the time of ovulation and can be used as a predictor of ovulation.

**Oligomenorrhea:** Infrequent menstruation, menses are greater than 35 days apart.

**Orgasm:** The climax of sexual excitement.

**Osteoporosis:** Atrophy of bone caused by demineralization.

**Ovulation, induction of:** Stimulation of ovulation by artificial means.

**Papanicolaou smear (Pap smear):** A cytologic smear of exfoliated cells (for example, from the cervix, endometrial cavity or vagina) used in the early detection of cancer or for evaluation of a patient’s hormonal status.

**Pelvic floor:** The floor of the pelvic structures. Located at the level of the pelvic outlet. The most important structures are the levator ani muscle, but the piriformis and coccygeus muscles contribute, as well.

**Pelvic inflammatory disease (PID):** An infection of the pelvic viscera, usually by ascending routes. The likely etiologic pathogens include: Neisseria gonorrhoeae, Chlamydia trachomatis, and other anaerobic and aerobic organisms. Often the infection is polymicrobial.

**Perineorrhaphy:** Reconstructive repair of the perineum where the perineal body is rebuilt by reapproximating the Transverse Perineii muscles, the Bulbocavernosis muscles and the External Anal Sphincter.

**Perineum:** The pelvic floor and associated structures occupying the pelvic outlet. The connective tissue between the vagina and anus.

**Pessary:** A device placed in the vagina to support the uterus and pelvic floor.

**Pneumoperitoneum:** The presence of air in the peritoneal cavity.

**Polycystic ovary syndrome (PCOS or Stein-Leventhal syndrome):** A syndrome of secondary oligomenorrhea and infertility associated with multiple follicular cysts of the ovary and subsequent failure to ovulate. The irregular vaginal bleeding is “anovulatory” in etiology, resulting from higher levels of estrogen. Often patients are at risk for endometrial hyperplasia secondary to unopposed estrogen because they are not ovulating regularly.

**Polymenorrhea:** Cyclical uterine bleeding that is normal in amount, but occurs <24 days apart.

**Postmenopausal bleeding:** Bleeding from the uterus, cervix or vagina that occurs after menopause.

**Premenstrual syndrome (PMS):** A complex of symptoms occurring in the progestational phase of the menstrual cycle, characterized by bloating, irritability, and mood changes.

**Puberty:** The period between the beginning of the development of secondary sexual characteristics and the completion of somatic growth.
Delayed: The lack of appearance of secondary sexual characteristics by age 14.

Precocious: The appearance of secondary sexual characteristics before 7.5 years of age. 
*The ages listed above are dependent upon a patient’s ethnicity.*

Rectocele: Protrusion of the rectum through the supporting structures of the posterior vaginal wall.

Reflux, tubal: The retrograde flow of uterine or tubal contents into the abdominal cavity.

Rhythm (periodic abstinence): A method of contraception in which coitus is avoided when ovulation is likely. This is also known as “Natural Family Planning.”

Salpingectomy: Surgical removal of fallopian tube.

Salpingostomy: Surgically incising the lumen of the fallopian tube in order to remove its contents (i.e. blood or ectopic pregnancy).

Salpingooophorectomy: Surgical removal of a fallopian tube and ovary.

Schiller test: The application of a solution of iodine to the cervix. The iodine is taken up by the glycogen in normal vaginal epithelium, giving it a brown appearance. Areas lacking in glycogen are white or whitish yellow, as in leukoplakia or cancer. Although nonstaining areas are not diagnostic of cancer, they aid in choosing the spot to which a biopsy should be directed.

Secondary sexual characteristics: The physical changes that have occurred in response to endocrine changes during puberty. Thelarche; Menarche; Adrenarche.

Semen analysis: The evaluation of the components of semen, especially spermatozoa, as a means of evaluating male fertility.

Sexual dysfunction: Any psychological, physiological, or anatomical disorder of the sexual cycle including the following phases: excitement, plateau, orgasm, and resolution.

Sexuality: The physiologic and psychologic expression of sexual behavior. The periods of infancy, adolescence, adulthood and the postclimacteric state each have characteristic manifestations of sexuality.

Sims-Huhner test (post coital test): A test for infertility in which cervical mucus is aspirated after coitus and examined for quality and presence or absence of infection. The motility, normality and number of sperm are noted, as well.

Skene glands: The vestibular glands that open into and around the urethra.

Somatomammotropin, chorionic: See Lactogen, human placental.

Sonography (ultrasonography, ultrasound): In obstetrics and gynecology, a diagnostic aid in which high-frequency sound waves are used to image pelvic structures in pregnant and non-pregnant patients.
**Spinnbarkeit:** The ability of the cervical mucus to be drawn out into a thread, characteristically greater in the preovulatory and ovulatory phases of the menstrual cycle.

**Sterility:** The absolute inability to procreate.

**Stress incontinence:** The involuntary leakage of urine during an increase in intra-abdominal pressure as a result of weakness of the supports of the internal vesical sphincter and bladder neck.

**Testicular feminization:** A syndrome of androgen insensitivity characteristics by primary amenorrhea, a female phenotype, testes (abdominal or inguinal) instead of ovaries, the absence of a uterus and a male genotype.

**Thecoma:** A functioning ovarian tumor composed of theca cells which produces androgens (testosterone).

**Thelarche:** The onset of development of breasts.

**Ultrasonography:** See Sonography.

**Ultrasound:** See Sonography.

**Urethrocele:** Protrusion of the urethra through the supporting structure of the anterior vaginal wall.

**Vasectomy:** The surgical interruption of the ductus (vas) deferens for permanent contraception in the male.

**Virilization:** The development of masculine traits in a female.

**Withdrawal bleeding:** Uterine bleeding after the interruption of hormonal support of the endometrium, typically obtained after a 10 day treatment with progesterone.

**BSO:** bilateral salpingo-oophorectomy
**BTL:** bilateral tubal ligation/fulgaration/cautery
**CX:** cervix
**DI:** detrusor instability ("bladder spasm")
**EFG:** external female genitalia
**ETOP/TAB:** elective abortion
**G:** gravidy
**HRT/ERT:** hormone/estrogen replacement therapy
**IUD:** intrauterine device
**IUI:** intrauterine insemination
**LAVH:** laparoscopic assisted vaginal hysterectomy
**LMP:** last menstrual period
**MMR:** menometrorrhagia
**OCP:** oral contraceptive pills
**P:** parity
**RV:** recto-vaginal
**SAB:** spontaneous abortion
**SUI:** stress urinary incontinence
Basic Science Highlights/Review:

Anatomy
-The vulva and vagina are lined with squamous epithelium. The vulva contains keratinized epithelium, and is hair-bearing. The vagina is nonkeratinized, and is non-hair-bearing.
- The cervix contains glandular and squamous epithelium. This transition zone (TZ) of metaplasia is a common origin for cervical dysplasia and is what is screened with cervical cytology.
- The endometrium contains glands and stroma.
- The ovary contains stroma and glands, and lesions may arise from either type of cell.
  a. Review the blood supply, nerve supply, and adjacent structures to the uterus, cervix, ovaries, and vagina and vulva
  b. Review the anatomy and innervation of the pelvic floor, which may be affected in pelvic organ prolapse.

Physiology
- The student should review the production of estrogen and progesterone by the ovary, including feedback loops involving the hypothalamus and pituitary gland. The student should also review the effects of estrogen and progesterone on the endometrium relative to the menstrual cycle. (This topic is summarized in the “Normal and Abnormal Bleeding” section.)

Selected Topics in Gynecology

The following items address common gynecologic issues affecting women.

Vaginitis
- **Bacterial vaginitis (BV)** is the most common vaginitis, responsible for 50% of vaginitis. BV presents clinically with malodorous vaginal discharge that has a pH greater than 4.5. Clue cells are observed on a saline wet mount.
- **Yeast vaginitis** accounts for 25% of vaginitis. Yeast vaginitis presents clinically with itching and irritation, and a thick curd-like non-odorous discharge. pH is between 4 and 5. Budding yeast and hyphae are observed on a KOH smear.
- **Trichomonas vaginitis** accounts for 25% of vaginitis. Trichomonas presents clinically with a greenish vaginal discharge, nonodorous, and motile flagellated trichomados are observed on a saline wet mount.
<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>BV</th>
<th>Candida</th>
<th>Trichomonas</th>
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<tr>
<td><strong>pH</strong></td>
<td>3.8-4.2</td>
<td>&gt; 4.5</td>
<td>&lt; 4.5</td>
<td></td>
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<td><strong>Discharge</strong></td>
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<td>gray white</td>
<td>“curdy”</td>
<td>green-yellow, frothy</td>
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<td>Fishy + Whiff Test</td>
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<td>? fishy</td>
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<tr>
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<td>Odor</td>
<td>itch/burn</td>
<td>irritation</td>
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</tbody>
</table>

**Contraception**

- *Combination hormonal contraception* includes oral (oral contraceptive pills or OCP’s), transdermal (Ortho Evra), or vaginal (Nuva Ring) routes of administration. Combination hormonal contraception works by suppressing ovulation, creating a thick cervical mucus barrier, and thinning the endometrium and affecting tubal transport. Failure rates are <1% if used properly. Progesterone-only methods are also available, including oral, IM, and subdermal implants as routes of administration.

- *Barrier* methods do not contain hormones, but work by actively preventing communication between sperm and an oocyte. These methods are associated with the highest failure rates. Examples include condoms and diaphragms.

- *Intrauterine Devices* (IUD) include non-hormonal and progesterone-containing. High success rate and do not require active work by the user, so compliance is greater. Potential complications include uterine perforation, infection, and expulsion.

- *Sterilization* includes tubal ligation, tubal occlusion (Essure), or vasectomy. Intended to be permanent, require a procedure, and are not 100% effective. (Approximately 99.3% effective.)

- *Emergency Contraception (EC)* when taken within 72 or 120 hours depending on the type, hours, decreases conception rates by 75%. Side effects may include nausea. Very effective and useful for patients without any contraceptive method, unexpected intercourse, broken condom, etc. In some states, this is available over the counter without a prescription. EC does not interrupt an already established pregnancy, nor is it an abortifactant. EC can be dosed with progesterone only pills or combination estrogen and progesterone pills.

**Pelvic Relaxation**

- *Cystoceles* form when the bladder prolapses against a weakened anterior vaginal wall. Symptoms may include bulging, inability to empty bladder.

- *Rectoceles* form when the rectum prolapses against a weakened posterior vaginal wall. Symptoms may include bulging and pressure, an inability to defecate, and a
need to place finger into the vagina and push posteriorly to assist with bowel movements (splinting)
- **Cervical and uterine prolapse** occur when there is a loss of structural support of the uterus, particularly of the uterosacral and cardinal ligaments. Symptoms include bulging, pressure, and low back pain.
- **Treatment** can be surgical or by insertion of a *pessary* in addition to pelvic floor exercises (Kegel exercises).

**Urinary Incontinence**
- Urinary incontinence may be urge, stress, overflow, intrinsic sphincter deficiency or mixed incontinence.
- **Urge incontinence** (also referred to as “overactive bladder”) is a result of detrusor overactivity, resulting in a sensation of frequency and urgency, with loss of large volumes of urine associated with a sensation of needing to void. Treatment is with anticholinergics to reduce detrusor contractions.
- **Stress incontinence** is a result of loss of urethral support, resulting in hypermobility of the urethra. Symptoms include leakage of small amounts of urine associated with an increase in abdominal pressure, or Valsalva maneuvers. Patients complain of leakage of urine with cough, sneeze, laugh, jumping, or exercising. Treatment may be with Kegel exercises, pessary, or surgical.
- **Overflow incontinence** results from neurologic insult and an inability to sense that the bladder is full. Patients report continuous leakage or constant dribbling, and usually have a history suggesting potential for neurologic insult. Treatment may require intermittent self-catheterization.
- **Intrinsic Sphincter Deficiency** results from a loss of urethral sphincter function. Symptoms may be similar to stress incontinence, but the patient may not exhibit hypermobility of the urethra.
- **Mixed incontinence** contains components of both urge and stress incontinence.
- **Evaluation** involves simple or complex cystometrics which evaluate bladder storage, bladder emptying, and urethral function. The information obtained can then differentiate between the various types of incontinence. A detailed H and P is also vitally important to differentiate the various types of incontinence.

**Endometriosis**
- **Endometriosis** results from endometrial glands and stroma implanted in areas outside of the endometrium. Patients may have chronic pain or infertility.
- There are many appearances to endometriosis. Evaluation involves taking a complete history, including symptoms that may be consistent with endometriosis. An exam is integral, as well, to determine the presence of pain at the uterus or adnexae. An ultrasound should be obtained to rule out other etiologies. Either diagnostic laparoscopy or a trial of medical management can be used to improve symptoms.
- Endometriosis is treated by suppressing endometrial activity, with combination contraception, gonadotropin releasing hormone agonists, or
surgically by ablating endometrial implants. More drastically, both ovaries can be removed, resulting in no further estrogen production. Low dosage HRT usually must be provided back to the patient, though, to protect bone health.

Infertility
- Affects 15% of people
- May result from anovulation, female structural problems (i.e. tubal occlusion, pelvic adhesions or absence of tubes, etc.), spermatogenesis or motility problems, and is unexplained in 10%
- Evaluation: Complete history and physical (H&P). Laboratory studies include Cycle Day 3 LH and FSH levels (Day 3 of menstrual cycle with Day 1 being the first day of bleeding). This evaluates hormone production and ovulation. Having the patient keep a menstrual chart will determine the regularity of her menses. Semen analysis assess sperm function and presence. Radiologic studies include a hysterosalpingogram (HSG) to assess tubal patency and the uterine cavity. An ultrasound can assess for gross anatomic abnormalities such as a pelvic mass.
- Treatment: Ovulation induction can be achieved with Clomid (clomiphine citrate). Intrauterine insemination or other artificial reproductive technology (ART) such as in vitro fertilization (IVF). Sometimes donor egg or donor sperm need to be used. Additionally, tubal cannulization can be attempted surgically. Myomectomy can be done to remove intrauterine fibroids that are causing a mass effect in the uterine cavity preventing pregnancy.

Cervical Disease
- Screening test for cervical disease is a cervical cytology (informally referred to as a “Pap smear’’). The use of high-risk Human Papilloma Virus (HR-HPV) testing may also be incorporated into screening algorithms depending on the patient’s age. The interval for screening when using both cytology and the HR-HPV test is lengthened (currently up to 5 years).
- Varying degrees of abnormal cells are classified according to the Bethesda System
- Colposcopy provides for closer evaluation of cervix
- Dysplasia may be treated with ablation, excision, or simply observed in some cases.

Ovarian Disease
- Varying types of cysts can be categorized by epithelial, stromal, or germ cell origins
- Most common epithelial ovarian neoplasm is a serous cystadenoma
- Stromal tumors such as granulosa cell tumors, are functional cells and secrete hormones, leading to varying symptoms.
- Germ cell tumors are the most common type of malignant neoplasms in women under age 20. The most common germ cell tumor (nonmalignant) is a mature teratoma, or dermoid.
- Evaluation: Complete H and P. Radiographic studies include an ultrasound, which is the best way to characterize adnexal masses. Sometimes a follow up CT scan is necessary, but one should start with an ultrasound.

Treatment: Depends on malignant or benign state of mass, age, characteristics, and symptoms.
Summary / Take Home Points:

1. Vaginitis is a common gynecologic complaint. Varies etiologies exist and can be differentiated by symptoms, pH of the vagina, and examination of vaginal discharge grossly and microscopically.

2. Contraception is an important component of women’s health care. Many methods are available to suit individual patient needs.

3. Pelvic relaxation and prolapse are significant problems for women. These defects may be managed with Kegel exercises, pessaries, and/or surgery.

4. Urinary incontinence is a common complaint. There are various types of incontinence which can be differentiated by symptoms and examination. Treatment varies depending on the type of incontinence.

5. Infertility is a common problem in our country. The etiology can be determined based on a thorough history and physical, laboratory, radiographic, surgical findings. Treatment differs based on etiology.

6. Cervical cytology screening has reduced cervical cancer significantly. Varying types of abnormalities exist, and indicated varying degrees of dysplasia. Evaluation with colposcopy and biopsy aids in diagnosis of dysplasia. Treatment may be observational, ablative, or excisional in nature.

7. Ovarian neoplasms are most commonly benign. Neoplasms may be of epithelial, stromal or germ cell origin.
Practice Questions/Answers

1. The definition of urge incontinence is:
   A. incontinence due to loss of urethral support
   B. incontinence due to detrusor overactivity
   C. incontinence due to the inability to sense a full bladder
   D. incontinence due to loss of urethral sphincter function

2. Which type of contraception is user-dependent?
   A. oral contraceptive pills
   B. IUD (intrauterine device)
   C. vasectomy
   D. bilateral tubal occlusion

3. A 34-year old asymptomatic woman is found to have a 6 cm mass on pelvic examination. Subsequent ultrasound reveals a 5.5 cm simple-appearing left adnexal cyst. What is the most appropriate next step?
   A. surgical exploration and oophorectomy
   B. CT scan
   C. serum CA-125 measurement
   D. observation

4. A 33 year old woman, G0, has been unable to conceive for the last 18 months. She describes regular menses. Her past history is only significant for an episode of pelvic inflammatory disease at age 20. Her husband of 5 years has a child from a former marriage how is 10 years old. What is the most likely reason for her infertility?
   A. male factor
   B. ovulatory dysfunction
   C. tubal obstruction
   D. cervical stenosis

Answers:
1. A (incontinence due to detrusor overactivity): The bladder muscle (detrusor muscle) contracts irregularly, causing an urge sensation and need to void immediately, otherwise the patient will experience incontinence. Stress urinary incontinence is loss of urethral support which can progress to loss of urethral sphincter function (a continuum) where an increase in intra-abdominal pressure will overcome the closing pressure of the urethra and cause incontinence. Overflow incontinence is due to the inability to sense a full bladder secondary to neurologic injury to the bladder.

2. A (oral contraceptive pills): The effectiveness of oral contraceptives depend on regular usage. If pills are missed, the efficacy significantly decreases and failure can occur. IUD's are placed by the physician in the office setting, into the patient’s uterus. Once placed, the patient does not play a role in its use or subsequent efficacy. Once a vasectomy is completed and tested (semen analysis documenting no sperm), and once a
bilateral tubal occlusion is performed, efficacy does not change relative to the patient’s activities or use.

3. D (observation): In a premenopausal woman with a simple cyst, the most likely etiology is either a functional cyst related to follicular development or ovulation, or a benign epithelial neoplasm. Without significant symptoms, the most appropriate course of action would be observation, with a follow-up; ultrasound in 3 – 6 months to assess for persistence (most likely a benign epithelial neoplasm) or resolution (functional cyst). Even in postmenopausal women, small (< 6 – 8 cm) simple cysts may be observed. Complex cysts on ultrasound raise suspicion, particularly in menopausal women, and would more likely result in surgical exploration. CA-125 is a tumor marker useful in potentially the diagnosis, but more so in follow-up, of menopausal women with adnexal masses; its use in premenopausal women is of minimal value.

4. C (tubal obstruction): Although male factor infertility is one of the most common etiologies for infertility, the fact that the husband has previously fathered a child makes male factor less likely. With regular menses, it is likely that she ovulates regularly, although verification of ovulation would be important in this patient’s work-up. Cervical stenosis is rarely a factor in infertility. A history of pelvic inflammatory disease is associated with a 14-fold higher likelihood of infertility due to tubal damage, which may include tubal obstruction and/or dysfunction.
Normal and Abnormal Uterine Bleeding

Introduction:
Abnormal uterine bleeding is one of the most common reasons a woman seeks care relative to a gynecologic issue. It is important to understand the normal hormonal milieu and its effects on the endometrium, resulting in normal cycles. A good understanding of normal menstrual physiology allows one to develop a differential diagnosis and diagnostic and management plan for women with abnormal uterine bleeding.

Evaluation of women presenting with abnormal bleeding therefore involves several considerations, including:
1. What is this patient’s normal bleeding pattern?
2. How would you characterize her current bleeding pattern?
3. How long has the abnormal bleeding pattern been present?
4. Is the patient at risk for a uterine neoplasm as an etiology of the bleeding?
5. What is the best approach to evaluation?

Readings: The following reference provides a good resource regarding normal and irregular menses:


Objectives:
At the end of this session, students will be able to:
1. Describe physiology and endocrinology of the normal menstrual cycle
2. Distinguish between normal and abnormal uterine bleeding
3. List and differentiate causes of abnormal uterine bleeding
5. Describe therapeutic options for uterine bleeding

Reference and Background Materials
The following section of the syllabus will provide the student with comprehensive information regarding labor and delivery considerations.

Key definitions and Acronyms: (NOTE: Numerous definitions and acronyms applicable to this section were already listed in the previous section)

Endometrial biopsy: The procedure of obtaining endometrial tissue for diagnostic purposes. This is an office procedure requiring no anesthesia.

Estrogen, unopposed: The continuous and prolonged effect of estrogen on the endometrium, resulting from a lack of progesterone. This is associated with an increased risk of endometrial cancer.
Pituitary: An endocrine organ composed of the anterior gonadotropin secreting component and the posterior oxytocin secreting component.

Basic Science Highlights/Review:

Anatomy:
- Review the blood supply, nerve supply, and adjacent structures to the uterus, cervix, ovaries, and vagina and vulva
- Review the anatomic changes in the endometrium throughout the menstrual cycle.

Physiology:
- Review the hormonal production of the ovaries – estrogen and progesterone.
- Review the hypothalamic/pituitary/ovarian axis.
  - Hypothalamus releases GnRH in a pulsatile fashion.
  - GnRH causes anterior pituitary to release LH and FSH.
  - LH stimulates the ovaries to produce progesterone.
  - FSH stimulates the ovaries to produce estrogen.

Normal Menstrual Cycle:
- Basic functional components
  - Hypothalamic-pituitary unit
  - Ovaries
  - Uterus-endometrium
- Normal Parameters
  - Normal menstrual cycles 28 ± 7 days
  - Duration of menstrual flow 4-7 days
  - Average blood loss 30-45 ml. Menorrhagia is bleeding greater than 80 ml.
  - Ovulatory bleeding is cyclic and predictable
- Follicular Phase
  - Rapid endometrial growth due to stimulation by ovarian estrogen
  - Regeneration in region of glandular stumps
  - Maximum thickness of endometrium in late follicular phase
- Luteal Phase
  - Dependent upon ovulation (day 14) and development of corpus luteum, progesterone production
  - Progesterone inhibits further endometrial thickness because it is a stabilizing agent.
  - Microvasculature becomes well-differentiated (spiral arterioles)
- Menstrual Phase
  - Fall in progesterone as corpus luteum involutes when pregnancy is not present.
  - Vasoconstriction >ischemia and hemorrhage
  - Release of PGF 2a, hence why NSAIDs are useful to treat menorrhagia.
  - Hemostasis
- Hormonal changes
  - LH peaks day 14, thus LH can be used to predict ovulation.
- FSH slightly increased day 14 and 27-28  
- Estradiol peaks day 12-13  
- Progesterone peaks day 18-22 then falls  
- Inhibin increased in luteal phase

**Differentiating Types of Endometrium:**

**Menstrual Endometrium**
- Thin, dense, nonfunctioning basalis  
- Small residual stratum spongiosum  
- ~2/3 of functioning endometrium lost during menses

**Proliferative Phase Endometrium**
- Period of increased estradiol secretion secondary to follicular development  
- Glands increase in number, link together with bridges  
- Thickness increases to ~ 5 mm

**Secretory Phase Endometrium**
- Height fixed despite continued estrogen secretion secondary to progesterone secretion. Progesterone functions as a stabilizing agent.  
- Individual components keep growing but are confined in a fixed structure leading to more tortuosity of glands and vessels

**Abnormal Uterine Bleeding**

**Definitions:**

- Dysfunctional uterine bleeding - a variety of bleeding manifestations of anovulatory cycles without a demonstrable organic cause. This is a diagnosis of exclusion.  
- Menorrhagia – prolonged or excessive uterine bleeding > 7 days occurring at regular intervals, or >80 ml.  
- Metrorrhagia – uterine bleeding occurring completely irregularly at frequent intervals, amount variable  
- Menometrorrhagia- prolonged bleeding occurring at completely irregular intervals  
- Polymenorrhea- bleeding occurring at regular intervals of less than 24 days  
- Intermenstrual bleeding- bleeding between regular menstrual periods  
- Oligomenorrhea- bleeding at intervals > 35 days  
- Premenstrual spotting- scanty bleeding occurring a few days to a week before menses  
- Postmenopausal bleeding- bleeding occurring greater than one year after the last menses in women with ovarian failure

<table>
<thead>
<tr>
<th>Term</th>
<th>Interval</th>
<th>Duration</th>
<th>Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligomenorrhea</td>
<td>prolonged (&gt;35 days)</td>
<td>varies</td>
<td>varies</td>
</tr>
<tr>
<td>Polymenorrhea</td>
<td>short (&lt;24 days)</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Hypermenorrhea</td>
<td>regular</td>
<td>normal</td>
<td>heavy</td>
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<tr>
<td>Metrorrhagia</td>
<td>irregular</td>
<td>prolonged or normal</td>
<td>normal/heavy</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>regular</td>
<td>prolonged</td>
<td>heavy</td>
</tr>
<tr>
<td>Hypomenorrhea</td>
<td>regular</td>
<td>normal/short</td>
<td>light</td>
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</tbody>
</table>
**Considerations:**

**Patient Evaluation:**
- **History:**
  - Dates of bleeding and prior menstrual pattern
  - Presence or absence of pain
  - Severity/quantity of bleeding: clots, # tampons/pads and degree of saturation, pads per hour
  - History of prior episodes of similar abnormal bleeding
  - Pregnancy symptoms
  - OB/GYN history, contraception
  - Current medications
  - Trauma
  - History of easy bruising/bleeding, clotting problems or family history of such
  - Inquire about body image, dietary habits (i.e. anorexia nervosa)
  - Systemic illness
- **Physical Examination:**
  - weight, BMI
  - abdominal exam (mass, ascites)
  - pelvic exam:
    - vagina/vulva (atrophy, lesions)
    - cervix (polyp, prolapsing fibroid, neoplasm)
    - uterus (size, shape, mobility, pain)
    - adnexa (mass, pain)
- **Labs:**
  - CBC, HCG, LFT’s (possibly), coags (possibly), Fe panel, TFT’s
  - cervical cytology (if indicated)
- **Additional studies:**
  - Ultrasound
  - Endometrial biopsy (possibly)
  - Hysteroscopy/D&C (25% of patients with DUB will be found to have organic lesions, such as polyps or fibroids)

**Differential Diagnosis: Pregnancy-Related:**
- Spontaneous abortion
- Abruption
- Placenta previa
- Labor
- Unknown etiology
- Ectopic pregnancy

**Differential Diagnosis: Non-Pregnancy-Related**
- Endocrine:
  - Thyroid disorders
  - Abnormal estrogen/progesterone production or uterine response
  - Abnormalities to hypothalamic-Pituitary Axis
- Peri- or post-menopausal
- Neoplasm:
  - Cancer
  - Endometrial hyperplasia
- Anatomic
  - Fibroids
  - Polyps
- Hematologic
  - Coagulation disorders due to hepatic dysfunction or coagulopathy
    - von Willebrand’s particularly in young women

**Treatment Approaches:**

**Estrogen therapy:**
- Necessary when prolonged hemorrhagic desquamation leaves little residual tissue
- High dose oral or IV

**Progesterone therapy:**
- Will not be effective in situations where endometrium is significantly denuded
- If endometrium is significantly denuded, patient will require estrogen therapy
- Useful for estrogen-primed endometrium (particularly oligo-ovulatory conditions such as polycystic ovary syndrome or perimenopausal status)
- Oral, IM, or IUD (progesterone-containing)

**Combination therapy:**
- OCP’s: 1 pill tid or qid x 5-7 day then may taper
- Flow usually stops within 12-24 hours
- Warn patients to expect heavy flow 2-4 days after discontinuation
- Combination options are progestin-dominant relative to effects on the endometrium; longer use of combination methods usually result in thinning of the endometrium and lighter flow

**Surgery (not first line therapy):**
- D&C
- Endometrial ablation
- Hysterectomy

**Summary / Take Home Points:**

1. Rule out pregnancy related event
2. Consider coagulation defects
3. If atrophy is a consideration, the uterine cavity is likely to be lined only by thin, raw basalis which is unlikely to respond to progestin therapy alone
4. Don’t forget about the patient after bleeding is under control as DUB is likely to recur if not treated long term (i.e. OCP’s, cyclic progestin, Mirena IUD)
5. Curettage is not the first line of defense
6. Patients with recurrent bleeding episodes despite repeated medical therapy may have a submucous leiomyoma or endometrial polyp and deserve evaluation by ultrasound or HSG.

7. Although endometrial hyperplasia or cancer are more common in older women, any condition resulting in relatively unopposed estrogen exposure (obesity, oligo—ovulatory conditions such as polycystic ovary syndrome) should raise a concern for hyperplasia or cancer regardless of the patient’s age.
Practice Questions/Answers

1. What is menorrhagia?
   A. Regular menses that last greater than 7 days.
   B. Regular menses with intermenstrual spotting.
   C. Irregular menses with each menses lasting less than 7 days.
   D. Menses occurring less than every 24 days.

2. Ovulation kits utilized LH to predict ovulation because:
   A. FSH peaks at cycle day #14.
   B. LH peaks at cycle day #14.
   C. LH nadirs at cycle day #14.
   D. Progesterone peaks at cycle day #14.

3. A 20 year old woman, G0, has infrequent menses but recently has had nearly daily spotting for the last 3 weeks. She has no significant past medical history, She is a marathon runner. Urine hCG is negative. What is the most likely source of her abnormal bleeding?
   A. Leiomyomas
   B. Endometrial polyp
   C. Endometrial atrophy
   D. Endometrial hyperplasia

4. An 18 year old sexually active woman, G0, complains of heavy menses. Her menses have been described as “heavy” since menarche She is anemic, with a hematocrit of 30%. Her past history is otherwise unremarkable, and exam is normal. What is the most likely etiology of the heavy menses?
   A. Cervical dysplasia
   B. Coagulopathy
   C. Endocervical polyp
   D. Adenomyosis
**Answers:**

1. **A (Regular menses that last greater than 7 days):** Regular menses that lasts greater than 7 days is menorrhagia. Regular menses with intermenstrual spotting is “intermenstrual spotting.” Irregular menses that last less than 7 days each is metrorrhagia. Menses occurring less than every 24 days is polymenorrhea.

2. **B (LH peaks at cycle day #14):** Ovulation kits detect an elevated LH level, or the LH surge, to assist with predicting ovulation. With the LH surge, an ovum is released from the ovary and fertilization can then occur.

3. **C (endometrial atrophy):** Women who exercise excessively, such as running marathons, are often amenorrheic due to low body mass and lack of ovulation. These women are often hypoestrogenic due to lack of GnRH stimulation of the pituitary to release FSH normally. Due to the hypoestrogenic state, these women often have very thin and unstable endometrial linings, which can bleed spontaneously. Although these women don’t ovulate regularly, contraception is not guaranteed by the lack of ovulation. Control of the bleeding would be best achieved by a combined hormonal contraceptive; progesterone alone would not be effective since the endometrium is already atrophic.

4. **B (coagulopathy):** Young women describing a history of heavy menses, particularly if they are anemic, deserve evaluation for an underlying coagulopathy, with von Willebrand’s disease being the most common. In fact, heavy menses is often a presenting symptom for women diagnosed with a coagulopathy. Cervical dysplasia and cervical cancer can be associated with abnormal bleeding; indeed post-coital bleeding may be a symptom, but this would not be the most likely etiology in this patient with a long history of heavy menses. Endocervical polyps and adenomyosis may also be associated with abnormal menses, but are less likely in an 18 year old woman.
CHIEF COMPLAINT:
“I have pain in my belly and I feel really sick”

HISTORY OF PRESENT ILLNESS:

Private Carla Jones is a 19 year-old woman currently in Basic Training, whose last menstrual began one week ago, thirteen days later than expected. She presents today to sick call complaining of one and one-half day history of malaise, chills, feeling feverish, anorexia, and lower abdominal pain which has become intense over the past 6 hours. She had felt well enough to fulfill her training requirements yesterday but not today.

PAST MEDICAL HISTORY:

She experienced menarche at age 13. Her menses occur every 28-30 days normally. She began taking Ortho-Tri Cyclen 3 years ago to help with her painful periods and to control her mild acne. She had no problems with the pill, but failed to refill them six months ago. She has had no dysmenorrhea since then.

A review of PVT Jones' medical records reveals that she had a gynecologic examination 3 months prior, by her private physician prior to joining the Army. At that time she had mucopurulent endocervicitis, which was documented in the progress note. Since she was asymptomatic, she was not empirically treated at the time of the exam, and cultures were obtained. She was told to return or call back in 3 days for the results. She was busy preparing for her future career in the Army and forgot to seek the recommended follow-up.

REVIEW OF SYSTEMS: Otherwise unremarkable.

CURRENT MEDICATIONS: None.

PHYSICAL EXAMINATION:

-B.P 126/70, P-104, R-22, T-101.8
-Ht. 5'5, Wt. 132 lbs.
-The patient was observed protecting her lower abdomen with both hands as she shuffled slowly into the examination room. She appeared slightly pale but otherwise well developed.
-HEENT; normal.
-Examination of the breasts, heart, and lungs were normal.
The abdomen was slightly distended with hypoactive bowels sounds. There was diffuse moderate lower abdominal tenderness to palpation, right > left, but no rebound or guarding.

Pelvic exam revealed the vulva and vagina to be normal.
- Cervix was nulliparous. The endocervix was erythematous with a large amount of yellow mucoid discharge of the cervical os.
- Bimanual examination revealed the cervix to be tender with direct palpation and motion. The uterus was tender, but was mobile and anteverted, normal size, shape and consistency. There were no palpable adnexal masses. The adnexa were tender to palpation, right > left.
- The rectal revealed no masses, but confirmed tenderness in the posterior cul-de-sac.

SOME OF THE QUESTIONS TO BE CONSIDERED AS YOU PREPARE FOR THE MANAGEMENT OF THIS PATIENT INCLUDE:

1. What additional history would you like from the patient in order to further focus the differential diagnosis?
2. What additional studies should be ordered? What results would you expect?
3. What is your differential diagnosis for the patient described in this case? How would you as the primary care physician manage each diagnosis?
4. Would she require a referral? Hospitalization? Surgery?
5. What potential impact might this clinical problem have on her future gynecologic and reproductive health?
ASSIGNED READING:
Chapters 33 and 41

CHIEF COMPLAINT: “My periods have been heavy for 6 months and I bleed between periods”

HISTORY OF PRESENT ILLNESS:
Ms. Samantha brown is a 52 year old woman. She has been pregnant 3 times, with two term births and one spontaneous abortion. She had occasional heavy menses approximately 2 – 3 years ago which she attributed to approaching menopause. Since then, her menses, although slightly heavier, were fairly “normal” for her until about 6 months ago, when she stated to have spotting between menses and her menstrual flow became heavier. She denies pelvic or abdominal pain, and has not noted any other symptoms, including changes in bowel habits or diet. She has no history of rectal bleeding. She is sexually active. She was not previously evaluated for abnormal bleeding.

PAST MEDICAL HISTORY:
She experienced menarche at age 12. Her menstrual history was described above; her “normal” menses occurred every 28 – 30 days. She used oral contraceptives between ages 25 and 35 without difficulty. She has no history of abnormal cervical cytology, her last cervical cytology screening was 18 months ago. She underwent screening for diabetes two years ago and had a slightly elevated serum glucose, but she has not been evaluated further. She has “mild” hypertension for which she was able to control by increasing exercise and trying to lose weight; she has not required medications.

REVIEW OF SYSTEMS: Otherwise unremarkable.

CURRENT MEDICATIONS: Multivitamins

PHYSICAL EXAMINATION:
-BP: 138/88, P: 72, R: 18, T: 98.9
-Ht. 5'5, Wt. 198 lbs.
-HEENT: unremarkable
-Abdomen: obese; no masses or tenderness
-Pelvic:
  -normal external genitalia
  -normal vaginal exam; non-atrophic
  -cervix: without lesion, non-tender
  -uterus: slightly enlarged (8-week size) and irregular; mobile and non-tender
-adnexa: no masses but exam limited due to body habitus
-Remainder of exam WNL

LAB DATA:
-CBC:
  -WBC: 9,000
  -Hct: 35%
  -Plt: 220,000
-hCG: negative

SOME OF THE QUESTIONS TO BE CONSIDERED AS YOU PREPARE FOR THE MANAGEMENT OF THIS PATIENT INCLUDE:

1. What is your differential diagnosis?
2. Is there any additional history items you need to help prioritize your differential diagnosis?
3. How would you proceed with evaluation? What is the order of the next step(s) you would take to evaluate the patient?
4. What additional studies would you order?
5. How would you manage the patient provided your evaluation does not reveal an anatomic etiology?
Practice Case 1:
The newborn nursery staff calls you because they are concerned about a cyanotic infant. Baby Graham is a one hour-old male infant delivered by repeat elective cesarean section at 36 weeks to a 28 year-old mother whose prenatal history and course were uncomplicated. She was Group B Strep negative and her antenatal screening labs were otherwise normal. The membranes were ruptured at delivery and the amniotic fluid was clear. Nursing staff attended the delivery and report the infant was “doing great” and required only drying, stimulation, and oronasopharyngeal suctioning. After the C-section the staff took him directly to the nursery for routine postpartum care. At thirty minutes of life the nurse checked on him and found that he had respiratory distress, with retractions, tachypnea, and grunting. His blood glucose was 65. She suctioned his mouth and nose with a bulb followed by a suction catheter and the respiratory distress seemed to resolve. When she checked on him twenty minutes later he was again in respiratory distress. His pulse oximeter was 84%. She is concerned and would like you to come and assess the baby. What might be the cause of this newborn’s respiratory distress?

Practice Case 2:
You receive a second page regarding another infant born in the nursery. The nurse informs you that this full-term baby was born to a 25 year-old mother via vaginal delivery with an unremarkable prenatal course and negative maternal labs, including Group B Strep screen. Her initial APGAR scores were 9 and 9 at 1 and 5 minutes of life. At 4 hours of life, however, the baby appeared to be breathing fast when the mother tried to breastfeed her. When the nurse went to check on the infant, she noticed that the child’s lips appeared blue. A pulse oximetry probe was placed on the infant’s upper and lower extremities and both were found to be 79%. What could be causing this infant’s cyanosis?

Objectives: At the end of this section, the student should appreciate the following:

1. The differences between fetal and neonatal circulatory patterns.
2. The changes that must occur in order for an infant to transition from fetal to neonatal life.
3. Specific clinical conditions which alter the infant's ability to smoothly make this transition.

Readings: Current Diagnosis & Treatment: Pediatrics, 20th edition; access online via LRC. Assigned sections in Chapter 1: The Newborn Infant; Respiratory Distress in the Term Newborn Infant, Structural Heart Disease, Persistent Pulmonary Hypertension

Introduction: Profound changes in the circulatory and respiratory systems must take place in order for the fetus to successfully transition from intrauterine to extrauterine life. These dramatic changes allow the infant to rapidly switch from the placenta to the lung as the organ of respiration. However, transition isn’t limited to just the heart and lungs. The new postnatal
homeostasis requires a transformation in the function of most organ systems. This section will focus primarily on the cardiorespiratory aspects of transition. It will begin with a brief description of the intrauterine environment, the respiratory function of the placenta, and the fetal circulation pattern. The transition from intrauterine to extrauterine life will then be discussed, including a brief description of key events during labor that aid in this transition. Finally, common clinical situations of altered transition will be introduced.

The Fetal Environment
The placenta serves as the primary organ of respiration in the fetus. All oxygen exchange and carbon dioxide removal occurs within the placenta, and not the fetal lung. Therefore, blood is preferentially shunted away from the lungs and toward the placenta. The fetus obtains oxygen and nutrients from the mother through the placenta and umbilical cord.

Uterine blood flow (maternal side of placenta) is provided by uterine arteries. These uterine arteries lead to decidual arteries and eventually to the intervillous space where maternal blood bathes fetal vessels. Blood is then drained via decidual veins back to uterine vein. Umbilical blood flow occurs through umbilical arteries and veins. Umbilical arteries are paired and take relatively deoxygenated blood from the distal aorta to the placenta. A single umbilical vein then returns oxygenated blood to the fetus.

Placental gas exchange occurs at the level of the terminal villi where maternal blood bathes fetal blood vessels. Since fetal hemoglobin has a higher affinity for oxygen than does adult hemoglobin, diffusion of oxygen from the mother’s circulatory system to the fetus can occur. At this level, oxygen and carbon dioxide essentially pass down concentration gradients to achieve exchange. Maternal hemoglobin releases oxygen down a concentration gradient to the fetal circulation, which has lower oxygen tension. Carbon dioxide exchange essentially occurs in the opposite direction along a similar concentration gradient.

Blood from the placenta is carried to the fetus by the umbilical vein. A portion of the well-oxygenated umbilical venous blood returning to the heart from the placenta perfuses the liver. The remainder bypasses the liver through a shunt—the ductus venosus—and enters the inferior vena cava. The oxygenated blood in the inferior vena cava represents about two-thirds of the venous return to the right atrium. In the fetus, an opening between the right and left atrium—foramen ovale—allows about one-third of the vena cava blood to flow directly from the right to the left side of the heart and thereby bypass the pulmonary circulation. From the left atrium, blood flows to the left ventricle, where it is subsequently pumped to the coronary, cerebral, and upper extremity circulations. Venous return from the upper body combines with the remaining two-thirds of the vena cava blood in the right atrium and then flows into the right ventricle. The vast majority of the blood then enters the pulmonary artery from the right ventricle and bypasses the lungs through a patent ductus arteriosus (PDA) and enters the descending aorta.

Therefore before birth, only a small percentage (~8%) of a fetus’ cardiac output goes to the lungs. After birth, however, all of the cardiac output will go to the pulmonary circuit. High pulmonary vascular resistance is present in the fetus due to increased vascular tone in the resistant blood vessels of the pulmonary circulation.

The rapid change in the resistance of the pulmonary circuit is the key event in the transition from intrauterine to extra-uterine life. The lungs need to be both structurally and biochemically ready to provide adequate air exchange since they must function as the organ of respiration when the
placenta is no longer available. Alveoli serve as the primary air-exchanging units in lung.

Lung development, particularly alveolar development, occurs at a steady pace throughout intrauterine and into extrauterine life. Alveolar development occurs from approximately 24 weeks gestation through the 3rd year of life. The lungs are structurally able to provide adequate gas exchange with mechanical assistance at approximately 24 weeks gestation.

The primary physiologic stress in the air-filled alveolus is the marked surface tension that occurs at the air-liquid interface between alveolus and pulmonary epithelium and capillaries. This surface tension will cause alveolar collapse if not reduced. This reduction in surface tension occurs through the actions of surfactant.

Surfactant is a combination of surface-active phospholipids and proteins produced by Type II pneumocytes lining the alveolar space. This mixture reduces the surface tension at the air-alveolar interface and prevents alveolar collapse. Type II cell maturation and surfactant production begins at about 24 weeks gestational age and reaches normal neonatal levels at 37-38 weeks gestation. While alveoli and surfactant are present early in gestation, a fetus will not be able to support oxygenation and ventilation without support until near term gestation. Although measurement of the lecithin-sphingomyelin (L:S) ratio is a helpful determinant of fetal lung maturity, it cannot be performed as a test after birth since it requires amniotic fluid.

The Intra-partum Environment
The onset of labor causes significant alterations in the fetal environment and facilitates the many changes necessary to transition from intrauterine to extrauterine life. Labor plays an important physiologic role in this process, and fetuses that do not undergo labor may have more difficulty in transitioning from intrauterine to extrauterine life. Uterine contractions during labor cause changes in utero-placental blood flow. Normally, blood flow occurs to the placenta through the uterine arteries during both systole and diastole. As contractions increase in number and intensity, the diastolic component of utero-placental flow begins to diminish and may disappear completely. This reduction in uterine blood flow during contractions results in intermittent fetal hypoxia, transient acidosis, and hypercapnia. However, these changes are usually tolerated by the normal fetus.

During intrauterine life, there is a net efflux of fluid out of the fetal lungs. This efflux is driven by a chloride pump at the alveolar level which actively pumps chloride from pulmonary epithelium into the alveolar space. Water subsequently follows. As a result, the alveolar space is filled with fluid and there is a net production of fluid by the lungs during gestation. Near delivery and during labor, however, the activity of this chloride pump ceases. Fluid is then reabsorbed from the alveolar space into the pulmonary interstitium where it is carried via pulmonary lymphatics back to the thoracic duct and the circulation. Physical compression of the chest during vaginal delivery may play a role in clearing lung fluid, but this does not play as prominent a role as earlier thought.

The Neonatal Environment
A marked change in cardiorespiratory function must occur if an infant is to survive after delivery and the clamping of the umbilical cord. The two hallmark events of transition are the filling of the lungs with air and the marked decrease in pulmonary vascular resistance which subsequently increases pulmonary vascular flow.
The first breaths after delivery expand the alveolar units, establish functional residual capacity (FRC), and help clear residual lung fluid. Expansion of the lungs is also a stimulus for surfactant release from the Type II pneumocytes. Surfactant lowers the alveolar surface tension and stabilizes FRC.

A marked decrease in pulmonary vascular resistance is associated with the onset of ventilation (i.e. expansion of the lungs). This is likely a result of the anatomic location of resistant pulmonary vessels in the pulmonary interstitium. Expansion of the collapsed lungs with air tethers open these vessels and results in decreased resistance and increased blood flow. The PaO2 is rapidly increased with the onset of air-breathing. This increase in oxygen tension is accompanied by further decrease in pulmonary vascular resistance, likely secondary to a nitric oxide-mediated mechanism.

Shortly after delivery, there is marked diminishment in placental, and subsequently umbilical vessel blood flow. Removal of the low-resistance placenta from the systemic circulation increases systemic vascular resistance. As umbilical vein blood flow diminishes, there is decrease in blood flow through the ductus venosus. The ductus venosus subsequently closes.

Right atrial pressure decreases with the lowering of pulmonary vascular resistance, and left atrial pressure increases with increasing systemic vascular resistance. Therefore, the foramen ovale functionally closes. It is often anatomically patent for a prolonged period of time after delivery.

The ductus arteriosus contains contractile tissue, which is responsive to the oxygen content of the blood. As PaO2 increases, this tissue contracts and functionally closes the ductus arteriosus. The vessel then scars down over a number of weeks until it is completely obliterated.

**Examples of Altered Transition**
Neonatal transition usually occurs in relatively uneventful fashion. However, problems may occur at any step of the process. A few examples are listed below:

A. Transient tachypnea of the newborn (TTN)
   - marked by abnormal clearance of lung fluid from the alveolar space.
   - the retained fluid causes respiratory distress (tachypnea, grunting, and nasal flaring).
   - chest X-ray marked by "wet" appearing lung fields with evidence of increased interstitial and vascular fluid.
   -typically resolves within 24-48 hours.

B. Persistent pulmonary hypertension (PPHN)
   - occurs when the pulmonary vascular resistance does not appropriately decrease after birth.
   - pulmonary vascular tone may remain elevated for a variety of reasons to include meconium aspiration, pneumonia, birth asphyxia, and diaphragmatic hernia
   - blood is shunted across the foramen ovale and ductus arteriosus from the right side of the heart to the left side. Blood effectively bypasses the lungs, and as a result deoxygenated blood returning from the body returns to the arterial system without being oxygenated.

C. Patent ductus arteriosus (PDA)
   - characterized by a failure of the ductus arteriosus to respond to normal physiologic
stimuli and close shortly after birth. This is typically a disorder of premature infants, but it is also seen in a small percentage of term infants.
- as pulmonary vascular resistance drops after birth, the PDA becomes a channel for blood to pass from the aorta to the pulmonary artery. This is opposite to the direction blood flows through the ductus arteriosus during fetal life.
- the increased blood flow can eventually cause pulmonary edema and congestive heart failure.

D. Respiratory distress syndrome (RDS)
- primarily a disorder of premature infants since they have a deficiency in the amount of surfactant produced by Type II pneumocytes.
- rarely occurs in term infants, except in the presence of maternal diseases like diabetes.
- surfactant deficiency results in alveolar collapse secondary to increased surface tension at the air-fluid interface. The clinical presentation includes hypoxemia, hypercarbia, and respiratory distress.

E. Infection
- Intrapartum transmission of maternal rectovaginal flora such as Group B Strep and *E. coli* may occur during the passage of the infant through the birth canal or as an ascending infection following rupture of membranes. Clinical manifestations of neonatal infection can mimic many of the problems of transition, and should be included in the differential diagnosis.

Let’s now return to our patients…

**Practice Case 1:**
You realize that this cyanotic infant in respiratory distress is having difficulties transitioning. After consideration of the problem and differential diagnosis you ask the nurse to place the baby on facemask oxygen and to get a chest radiograph. To your examination the infant is in moderate respiratory distress with grunting, flaring, retractions and tachypnea. On facemask blow-by oxygen the saturation on the right-lower extremity pulse oximeter is 92%. There is no heart murmur, the infant is well-perfused and there are no other significant physical exam findings. You confirm the mother’s dates to be 36 weeks, and on physical assessment he has characteristics of a late preterm infant. Your concerns include transient tachypnea/retained fetal lung fluid due to lack of labor, respiratory distress syndrome (RDS), infection/pneumonia, pulmonary structural anomaly, pneumothorax/pneumomediastinum, or cyanotic congenital heart defect. To help sort this out, you ask that the infant be placed under a 100% oxyhood and ask for a CBC/differential, blood culture, and arterial blood gas. Given the respiratory distress, you also ask for an IV and an infusion of IV dextrose 10%. Under the oxyhood, the infant’s saturation improves to 98% though he remains tachypneic. His CBC and differential do not suggest infection. His chest radiograph shows a structurally normal heart and no evidence of pneumothorax or pneumomediastinum. There are no infiltrates. There is diffuse, bilateral interstitial streaking and fluid in the fissures. You make the diagnosis of transient tachypnea of the newborn due to retained fetal lung fluid. This is likely secondary to delivery at 36 weeks without the benefit of labor. You explain to his parents that he will require oxygen and monitoring in a neonatal intensive care unit, and that in most infants the fluid will gradually clear over the course of a few days. You make arrangements for transfer to a NICU, and caution
the nursery nurses to keep him under the oxyhood because as a newborn infant with respiratory disease he is at risk for persistent pulmonary hypertension of the newborn.

**Practice Case 2:**
You take the infant to the neonatal intensive care unit next door for further evaluation and consider a disorder of the pulmonary, cardiac, hematologic, or even metabolic system. On exam, her temperature is 37.3°C, heart rate of 150/min, respiratory rate of 68/min, and a blood pressure of 68/40. You note that she is alert, with a non-dysmorphic face. You remember that peripheral cyanosis (acrocyanosis) is normal, but you become concerned when you observe central cyanosis involving the tongue and lips. She appears comfortably tachypneic with nasal flaring but no retractions or grunting. The lungs are surprisingly clear bilaterally. You detect a grade II/VI systolic ejection murmur at the left lower sternal border but no hepatosplenomegaly is noted. A chest radiograph is obtained and does not show an infiltrate or a pneumothorax. A CBC and electrolyte panel are unremarkable. You decide to perform a bedside hyperoxy test by placing the infant in a high concentration oxygen hood with 100% FiO2. Despite this, the pulse oximeter remains at 79% indicating a possible fixed right-to-left shunt of cyanotic congenital heart disease, severe pulmonary disease, or persistent pulmonary hypertension. Because the chest x-ray did not reveal pulmonary disease and the pulse oximeter was consistently 79% on both the upper and lower extremities, you suspect congenital heart disease. The pediatric cardiologist performs an echocardiogram with color-flow doppler and confirms the diagnosis of cyanotic congenital heart disease—transposition of the great arteries with a small ventricular septal defect and patent ductus arteriosus. A prostaglandin E1 drip is started to prevent closure of the ductus as the child awaits the arterial switch surgical repair at the local children’s hospital. You thus determine that the cyanosis is from the marked right-to-left shunting across the ductus arteriosus leading to mixing of desaturated venous blood with oxygenated blood in the systemic arterial circulation.

**Practice Questions:**

1. Which of the following is not an important contributor to the fall in pulmonary vascular resistance after birth?
   a. the first breaths expand the lungs and help clear fetal lung fluid
   b. surfactant release from type II pneumocytes increases alveolar surface tension, improving lung inflation, and stabilizing functional residual capacity (FRC)
   c. lung inflation helps to tether open pulmonary blood vessels
   d. lung inflation leads to increased intra-alveolar oxygen tension

2. Which problem associated with altered transition is more common in preterm vs term infants?
   a. patent ductus arteriosus (PDA)
   b. meconium aspiration
   c. persistent pulmonary hypertension (PPHN)
   d. congenital heart disease

23:6
3. You want to check if a 34 week premature infant who was born 2 hours ago may be at risk for developing Respiratory Distress Syndrome due to surfactant deficiency. Could you send a lecithin-sphingomyelin (L:S) ratio on this patient to determine fetal lung maturity?

4. Hypoplastic left heart syndrome is one type of congenital heart disease in which the left ventricle of the heart is severely underdeveloped and therefore too small to pump blood to the systemic circulation. Explain how the right ventricle might be able to provide blood flow to the systemic circulation shortly after birth in the absence of a functioning left ventricle.

5. Match the following based on key words:
   a. TTN          b.  RDS          c.  PPHN
      ___ resolves within 12 hours
      ___ infant of diabetic mother
      ___ meconium aspiration
      ___ 32 week gestation infant
      ___ GBS pneumonia
      ___ short labor or C-section

**Answers to Practice Questions:**

1. B. Surfactant decreases alveolar surface tension. This explains why premature infants, who have not produced enough surfactant, often suffer from Respiratory Distress Syndrome—a process characterized by a lack of surfactant and treated with exogenously administered surfactant.

2. A. While any of these conditions can affect any gestational age infant, a patent ductus arteriosus is significantly more common in preterm infants. Respiratory Distress Syndrome is also more common in preterm infants who lack sufficient surfactant production. In contrast, both meconium aspiration and persistent pulmonary hypertension are seen more commonly in full term or post-date infants.

3. No. Although measurement of the lecithin-sphingomyelin (L:S) ratio can be helpful in determining whether a premature infant may be at risk for RDS, it can only be performed as a test before birth since it requires an amniotic fluid sample collected via amniocentesis. If preterm delivery is considered necessary and the L:S ratio is low, then the mother may receive steroids prior to birth to improve the fetus’ surfactant production.
4. In hypoplastic left heart syndrome, the right ventricle must pump blood to both the lungs and the systemic circulation. Following birth, blood flows from the right ventricle into the pulmonary artery and then is able to reach the aorta via the large patent ductus arteriosus. Because blood flow to the body relies on the patency of the ductus arteriosus, serious disturbances occur when the ductus begins to close several days after birth and blood is unable to enter the systemic circulation. Physicians must consider a “ductal-dependent” form of congenital heart disease in any infant with a sudden onset of cyanosis, hypoxemia, shock, and acidosis.

5. Match the following based on the key words:
   a. TTN          b. RDS          c. PPHN

   a  resolves within 12 hours
   b  infant of diabetic mother
   c  meconium aspiration
   b  30 week gestation infant with grunting
   c  GBS pneumonia
   a  short labor or C-section
ICR Neonatal Transition: Small Group Case Studies

CASE 1:

You are called by the nurse to see a 2 hour-old male infant in the Newborn Nursery. The baby weighs 3265 grams and is estimated by the mother's dates to be 41 weeks gestational age. The nurse reports that the infant has developed tachypnea with a respiratory rate of 80 breaths per minute. She also informs you that the infant has a bluish discoloration of his hands and feet.

1. What would you see as the patient's Chief Complaint?

2. What additional history would you like, and why?

3. What are some possible explanations for this infant's respiratory distress? (Differential diagnosis)

On examination, the infant's vital signs are: T = 37.2°C, HR = 145/min, respirations 80/min, and BP 65/40. Exam of the head, eyes, ears, nose and throat are normal. Breath sounds are heard and are symmetric.

4. What other physical findings would you be alert for?

5. Are there any laboratory tests you would order and why?

6. With the information you have, what is the most likely diagnosis?
CASE 2:

You are in the nursery evaluating an infant whose delivery you just attended. The delivery was by emergent C-section secondary to prolonged fetal bradycardia (heart rate 60-75 for 5 minutes). Thick meconium was present at time of rupture of membranes. The infant has a respiratory rate of 80-100 breaths/min. She is grunting with nasal flaring, and her lips are blue.

1. What would you say is the patient's Chief Complaint?

2. What additional history would you like to know and why?

3. What are some possible explanations for this infant's respiratory distress?
   (Differential diagnosis)

On examination, the infant's vital signs are: T = 37.5°C, HR=160/min, respirations 90/min, and BP 60/30. Pulse oximeter placed on right hand = 92%. Pulse oximeter placed on left foot = 79%. Exam of head, eyes, ears, nose, and throat are normal. Breath sounds are coarse bilaterally and prominent crackles are also heard.

4. What other physical findings would you be alert for?

5. Are there any laboratory tests you would order and why?

6. With the information you have, what is the most likely diagnosis?
CASE 3:

You are paged by one of the nurses about an infant who is only 2 hours-old who presents in respiratory distress. The nurse states that his tachypnea has progressively worsened over the past hour. His initial APGARS were 9 and 9. You review the chart and see that his estimated gestational age is 38 weeks and his birth weight was 4365 grams.

1. What would you say is the patient's Chief Complaint?

2. What additional history would you like to know and why?

3. What are some possible explanations for this infant's respiratory distress?  
   (Differential diagnosis)

On examination, the infant's vital signs are: T = 37.4°C, HR=155/min, respirations 70/min, and BP 65/34. Pulse oximeter reveals 84% (right hand) and 85% (left foot). Exam of head, eyes, ears, nose, and throat are normal. His tongue and lips have a bluish discoloration. Breath sounds are coarse bilaterally but chest rise is symmetric. You place the infant on 2L/min of oxygen via facemask prior to transporting him to the Neonatal ICU. His O₂ saturations improve to 93%.

4. What other physical findings would you be alert for?

5. Are there any laboratory tests you would order and why?

6. With the information you have, what is the most likely diagnosis?
Introduction to Clinical Reasoning

DEVELOPMENTAL DELAY
Christopher R Kieling, MD
Matthew D Eberly, MD

Practice Case 1:
Your 1030 patient is running a little late this morning, providing you with some extra time to read through her chart. This will be your first visit with this family, and they are bringing in their newly adopted girl from China for her 2 year well visit. They have told the nurse they just want to make sure her immunizations are up-to-date and that she is ‘developing’ normally.

Practice Case 2:
The next patient of the day is a 2 year-old presenting for his annual well-child visit. His family recently moved to the area and the child was last seen by a physician at the 18 month visit. At that time, his parents expressed concern that he only babble and did not have any words besides 'mama.' A hearing test performed after that visit was reportedly normal according to the parents. The mother and father appear worried about their son’s speech at today’s visit. What questions do you have for the family?

Objectives: By the end of this session, the student should:
1. Describe, in general terms, the process of normal childhood development
2. List the four domains of development and recognize normal and abnormal milestones for each

Readings: Current Diagnosis & Treatment: Pediatrics, 20th edition; access online via LRC.
Assigned sections in Chapter 2: Child Development and Behavior; Normal development: The first 2 years, Ages 2-4 years; Well Child Surveillance and Screening: Developmental Disorders, Autism Spectrum Disorders, Specific Forms of Intellectual Disability and Associated Treatment Issues

Introduction:
The process of development begins in utero and proceeds throughout childhood and adolescence. When it is normal, it is a seamless progression, and each child may be perceived by his parents as being "above average." Sometimes, when there are discrepancies between the expected development and the progress of the individual child the parent may notice and become concerned. This, however, may not always happen. One of the responsibilities of the physician caring for children is to monitor the development of each child and intervene appropriately to identify and evaluate potential delays in the normal developmental sequence.

To do this effectively it is important to know what is normal. Until you learn the milestones, the Denver Developmental Assessment (Denver II) graphs are a useful adjunct and a readily available referral source (these are included in your packet--be sure that you understand how to
use them). It is also important to state that the observation and evaluation of development begins, as does everything else in medicine, with a careful and complete history and physical examination. This compulsive and structured beginning may well be more important in this area of medicine than in many others.

**Variations in normal:**
It is clear that there are fairly wide variations in the level of skill that is expected for a given child at a given age. The task is to distinguish what is "maybe" outside the norm from what is "clearly" outside the norm. In the first case, careful monitoring and attention to relevant factors may be the only appropriate intervention. In the second case, it is important to determine the medical significance of the delay and institute appropriate measures to ensure that any consequences of the delay in development are minimized. Thus, there is a balance that must be maintained between not alarming a family about what will just turn out to be a variation of normal, on one hand, and missing an important clue to a problem for which effective intervention should be offered, on the other.

**Components of development:**
The normal development of a child is dependent not only on the function of every organ system, but also on the adequacy and appropriateness of the environment. Therefore, a delay in development may reflect an isolated defect intrinsic to the child, such as genetic problems in muscle function, or may reflect a deficiency in the child's environment, such as an inadequate diet, a lack of appropriate intellectual stimulation, or even exposure to an environmental toxin.

Most children with normal development experience an integrated progression from relatively helpless newborn to self-sufficient adult. In parallel, some children with delayed development have so-called "global delay" where no one area of development appears to be spared. However, it is more often the case that one area is affected out of proportion, or even exclusively, while development in other areas proceeds on schedule. The specific area affected and the lack of defects in other areas may provide valuable clues to etiology and may guide interventions.

Therefore, it is useful to consider development as composed of four distinct areas, each with its own series of milestones, acquired in a predictable sequence and at predictable times. When a milestone is not seen at an age where 90% of normal children would be expected to have attained it, this is referred to as a delay. A delay in a single milestone may not be of significance, but would always be an indication for an examination for a possible cause, for other possible related issues, and for close follow-up.

The four major areas of normal development are assessed at each scheduled well-child visit, and are also routinely, if only informally, noted at visits for acute problems. Although there is some overlap between areas, it is useful to consider each independently when evaluating the development of a given child.

The areas of development usually monitored include:

- **Gross motor** - Includes milestones such as sitting alone, rolling over, and walking.
- **Fine motor** - The use of the hands for manipulating the environment and eventually
Language/speech - Begins with the earliest "babbling" and progresses through the effective use of language for communication. Receptive language usually develops more rapidly than expressive language.

Personal/Social - Begins with regarding the parent's face, and progresses through smiling and imitative play.

See Table 2-1 in Current Diagnosis & Treatment: Pediatrics for a useful diagram of common Developmental Milestones. A few examples of developmental milestones include:

- **Gross motor**: hold head up 45 degrees at 2 months; sit without support at 6 months; walking at 12 months
- **Fine motor**: develop pincer grasp (i.e. pick up a cheerio) by 12 months; build tower of 4 cubes around 18 months
- **Speech**: Babbling begins by age 6 months; “mama” or “dada” nonspecific at 9 months; one word other than “mama” or “dada” around 12 months; two-word phrases by 18-24 months; Intelligible speech (to a stranger, not parent) as a fraction of 4
  
  i.e. 1/4 -- children age 1 will have 25% intelligibility
  2/4 -- children age 2 will have 50% intelligibility
  3/4 -- children age 3 will have 75% intelligibility
  4/4 -- children age 4 will have 100% intelligibility
- **Personal/Social**: wave bye-bye around 9 months; point to named objects or pictures around 18-24 months; engage in parallel play by 24-36 months

Recently, some experts have divided up child development into five domains: Motor/Physical, Cognitive, Social/Emotional, Communication/Language, and Adaptive/Self-help. Regardless, each one of these must be carefully addressed at each well-child appointment to ensure that the child is developing appropriately.

During the developmental assessment of a child, certain physical exam findings can raise red flags and alert the physician of a possible anomaly. For example, persistent fisting at 3 months of age often is the earliest indication of neuromotor dysfunction. Spontaneous postures such as the frog leg position provide visual clues to poor tone or weakness, while scissoring may indicate spastic hypertonia. Early rolling and persistent toe walking may be signs of spasticity as well.

A developmental delay might be the first indication of an underlying disorder. The etiologies behind delays are numerous. They may be due to genetic factors (Down Syndrome, Fragile X syndrome), complications during pregnancy (in utero CMV infection), environmental influences (lead poisoning), perinatal factors (birth asphyxia), maternal factors (fetal alcohol syndrome), metabolic disorders (galactosemia), or even neglect and malnutrition.

Whenever there is a language delay, a hearing deficit must be considered. Therefore all children whose speech is delayed should receive a screening audiology exam.

And finally, regression of any skills is always considered abnormal and warrants investigation.

Of note, due to the apparent rise of children affected by autism spectrum disorders, physicians
should remain vigilant about identifying possible abnormal social behaviors during well-child visits. Children with autism have significant impairment in the ability to relate to people, including their parents. They may prefer solitary play and remain uninterested in communicating with others. Those with autism characteristically display stereotypic, compulsive, and ritualistic behaviors.

**Early intervention:**
After identification of a delay in development, it is common to institute a plan for amelioration of any possible delay. This might involve hearing aids and speech therapy for a child with speech delay secondary to defects in hearing or physical therapy for a child with gross motor problems. It is a tenet of pediatrics that early intervention may be effective in minimizing the effects of development delay in many but not all cases.

The assigned text should be a useful resource for approaching the evaluation of a child with questionably or definitely delayed development. Working through the cases, using the textbook chapter, first alone, and then with your preceptor and small group will be a good introduction to this important area of pediatrics.

**Let’s now return to our patients…**

**Practice Case 1:**
Your 1030 patient is running a little late this morning, providing you with some extra time to read through her chart. This will be your first visit with this family, and they are bringing in their newly adopted girl from China for her 2 year well visit. They have told the nurse they just want to make sure her immunizations are up-to-date and that she is ‘developing’ normally.

After conducting a thorough history including past medical history, birth history, medications, and immunizations, you turn your focus to the child’s development. Before entering the room, you were able to glance at the developmental milestones expected for her age. You correctly recall that there are 4 domains, and begin by asking questions about her gross motor development. Parents report she is walking, running, walking up and down stairs, and is able to throw a ball overhand. For fine motor skills, you have her stack blocks in your office. She easily stacks 6 blocks, and parents report she is ‘brushing her teeth’ and starting to be able to put her clothes on. So far so good, you think. Assessing her speech is a little more challenging. She has only been in the U.S. for a couple of weeks, and was exposed to only Chinese while in China. You remember that the average 2 year old should be able to put two words together in a sentence and should have a vocabulary of around 200 words. Their speech should also be 50% intelligible to strangers. She is somewhat shy in the office today, so you elect to discuss these milestones with the parents and watch to see how things go for the next few months. You will reassess her speech when you see them back in 3 months for a follow-up. You plan on ordering a hearing test if her speech is indeed delayed at that time.

**Practice Case 2:**
The next patient of the day is a 2 year-old presenting for his annual well-child visit. His family recently moved to the area and the child was last seen by a physician at the 18 month visit. At that time, his parents expressed concern that he only babbled and did not have any words
besides ‘mama.’ A hearing test performed after that visit was reportedly normal according to the parents. The mother and father appear worried about their son’s speech at today’s visit. What questions do you have for the family?

You are concerned about this 2 year-old with intact hearing and significant speech delay and want to know if he has any other developmental delays, particularly in his gross motor skills, fine motor skills, and social/cognitive areas. The parents tell you that he was the product of a normal pregnancy and delivery. The mother denies any prenatal illness, medication use, alcohol use, or substance abuse. The boy had a normal newborn course and normal newborn screening. Looking through his chart, he met his gross motor and fine motor milestones on time. Although he follows simple commands in your office, the mother, however, states that he is not communicative with other children or adults and consistently avoids eye contact. He is frequently irritable and hyperactive at home. Upon asking about the family history, the parents report a learning disorder in the mother and an uncle with mental retardation. His physical exam is normal, aside from him being shy. You notice, however, that his head circumference is above the 90th percentile while his height and weight are both below the 25th percentile. Due to his delay in expressive language, possible abnormal social interaction, and family history of mental retardation, you elect to perform Fragile X testing, which comes back positive.

Fragile X syndrome is the most common single-gene cause of hereditary mental retardation; it is caused by a CGG trinucleotide repeat expansion in the FMR1 gene on the X chromosome. Children may display certain behaviors such as hyperactivity, social anxiety, and perseverative speech. Affected males can have characteristic facial features such as a large head circumference, long face, prominent forehead, large ears, and prominent jaw. These features are not always present in young children with Fragile X syndrome.

Practice Questions:

1. The average child begins walking at 1 year. At what age, should you be concerned if a child is not walking?
   a. 13 months
   b. 15 months
   c. 18 months
   d. 24 months

2. A child who has a well-developed finger-and-thumb pincer grasp, and is able to say ‘mama’ and ‘dada’ specifically to the correct parent, is most likely:
   a. 6 months old
   b. 9 months old
   c. 12 months old
   d. 15 months old

3. During the health supervision visit for an 18 month-old boy, his parents express concern that he is vocalizing but not saying any real words. The boy is holding a toy car and appears fixated
on spinning the car's wheels. When you call his name, he seems to ignore you. You point to a mirror above the sink and say "look," but he avoids any eye contact. Of the following, the most likely diagnosis for this boy is:

a. Mental retardation
b. Autism
c. Expressive/receptive language disorder
d. Obsessive-compulsive disorder
e. Down syndrome

4. During the well-baby visit of an infant, you begin your exam by placing her prone on the examination table. She is able to track your penlight, following it 180 degrees by lifting her head and shoulders off the table. Based on her gross motor exam, the age of the infant is most likely:

a. 1 week-old
b. 1 month-old
c. 2 months-old
d. 4 months-old
e. 6 months-old

5. You observe a child as he walks into the exam room. He is holding a small ball and gives it to you when you ask him for it. When you toss the ball back to him, he reaches to catch it but almost falls over. He is able to stack 2 blocks and can scribble on the exam paper using a crayon. Based on this encounter, what is the most likely age of your patient?

a. 9 months
b. 12 months
c. 15 months
d. 18 months
e. 24 months

**Answers to Practice Questions:**

1. B. Gross motor development follows a fairly predictable course wherein a child will roll from front to back at 4-5 months, sit alone at 6 months, pull to stand at 9 months, and walk by 12 months. A child that is not walking by 15 months is a red flag for gross motor delay.

2. C. This question focuses on both speech and fine motor development. A child develops a ‘raking grasp’ around 5 months, and begins to develop a pincer grasp by 9 months. By 12 months, a child should have a well-developed pincer grasp. Though a child might say ‘mama’ and ‘dada’ as early as 9 months, it becomes specific to the right person by 12 months.
3. B. This child has behaviors consistent with autism. Affected individuals have impairments in reciprocal social interactions, communication, and their range of activities or interests. The boy in this case does not make eye contact and is obsessed with the repetitive motion of the spinning wheels of his toy car. Children with autism may engage in repetitive play and demonstrate very little imaginative play.

4. C. Appropriate milestones for a newborn are limited to turning the head from side to side and fixating on a light in the line of vision. A 1 month-old infant may lift his or her head momentarily and follow a moving object. By 2 months of age, an infant in the prone position should be able to lift his or her head and shoulders off the examination table as well as regard and follow an object 180 degrees. A 4 month-old can lift up on his or her hands when in the prone position and may be able to roll front to back.

5. C. The child shows the normal motor developmental milestones for a 15 month-old, which consist of playing ball, giving and taking a toy, walking independently, drawing a line with a crayon, and building a two-cube tower.
ICR Developmental Delay Small Group Case Studies

CASE 1

A mother brings in her 13 month-old daughter for a checkup. She tells you that this appointment was made because of concerns that she is not walking. She states that her older sister who is now 4 years-old was walking well by 11 months of age and she wants to be sure that nothing is wrong with her child.

1. What is the chief complaint?

2. Does this child have motor delay? What are possible causes for gross motor delay? i.e. What is your differential diagnosis?

3. What additional history do you want?

4. What things will you look for on physical exam?
(CASE 1 continued)

Additional history reveals that she was a term baby, born at a normal size for gestational age, but has not grown very well for the past 4 months. She was exclusively breast fed until age 9 months. She continues to nurse, and eats a variety of baby foods, including fruits, vegetables, and meats. Her appetite is normal.

On physical exam, you find that she is a cheerful and cooperative 1 year-old African American girl, who is small for her age (less than 5th percentile for height and weight).

1. How would you approach this problem? What other history might be useful?

2. What other physical findings might you look for?

3. Are there any laboratory tests or radiologic studies that might be useful?
CASE 2

A mother has brought her 2 year-old son to the clinic for evaluation because of concerns that he is not talking very much. As you begin to examine him, she says that she tried not to be concerned because she knows that all children are different, but her older daughter was speaking in sentences by this age. She is worried because, not only is he not talking as well as his older sibling at this age, but he even seems to be regressing somewhat in his speech. She also mentions that he doesn’t like to be touched.

She notes he can be very difficult at times. She recalls one story in which he cried all evening after she rearranged the furniture in the living room.

1. What is the chief complaint?

2. Based on the history above, construct a problem list with your colleagues:

3. What additional history questions would you ask the parent?

4. If the patient were present, what would you pay special attention to on physical exam?

5. Based on the data from your history and physical and your problem list, what are the possible reasons for this child’s speech problem (Differential Diagnosis)?

6. Prioritize your differential, putting the diagnoses that explains most of the signs and symptoms and integrates with your problem list first, second, third, etc…

7. What laboratory or imaging studies would confirm the diagnoses on your list?
Introduction to Clinical Reasoning

PEDIATRIC ISSUES

Matthew D Eberly, MD

Practice Case:
Your first patient of the afternoon is a 5 week-old male infant who presents to clinic for vomiting over the past 6 days. The mother appears frustrated because her neighbor tried to convince her that it was due to “reflux,” but the spit-up seems to have progressively worsened. This morning her baby forcefully vomited up an entire volume of breast milk 15 minutes after he finished nursing. Despite the frequent vomiting episodes, the infant seems very interested in returning to the breast.

Overview:
Children are not simply little adults. They may share similar disease processes such as cancer or heart murmurs, or have similar presenting complaints such as abdominal pain or cough, but the clinical approach to the pediatric patient varies greatly from adults. Just within the field of pediatrics itself, the approach from child to child varies greatly depending on their age. The differential diagnosis for vomiting, for instance, is entirely different for a newborn than for a teenager. The following cases illustrate some unique aspects of clinical reasoning for the pediatric patient.

Back to the case...
The mother tells you her pregnancy and labor were uncomplicated and that they were discharged from the nursery within 48 hours of delivery. His 2 week well-baby exam was uneventful and his newborn screen came back normal. You ask the mother some more questions about her baby’s vomiting and discover that the infant’s emesis is non-bloody and non-bilious. You recall that non-bilious emesis in an infant is more likely to be from a more proximal obstruction, and therefore feel less concerned that it may be due to volvulus or intestinal atresia. You also consider acute gastroenteritis but the mother denies any sick contact or exposure to anyone with the “stomach flu.” She also denies fever or diarrhea in her child. Isolated vomiting in a newborn should also raise suspension for inborn errors of metabolism, urinary tract infection, toxic ingestions, or even increased intracranial pressure from a subarachnoid hemorrhage or meningitis. On the chart you notice his vital signs are normal: Temp 37.1˚C, HR 150/min, RR 42/min, BP 80/50, and SpO2 of 99% on room air. His physical exam is also benign and he appears well-hydrated. His head is normocephalic without evidence of trauma; his anterior fontanel is soft and flat; his lungs are clear and his respirations non-laborated; his heart exam is without murmur and his femoral pulses are strong; his abdomen is soft and non-
distended; his capillary refill is brisk and his skin is without petechiae, ecchymoses, or rash. Because the infant appears healthy, remains afebrile, and still has a strong interest in feeding, you place pyloric stenosis higher on your differential and order an abdominal ultrasound. The radiologist informs you that the infant has an elongated pyloric channel and an enlarged pyloric diameter of 15mm. You arrange to have the child admitted for pyloromyotomy surgery.

Practice Questions:

1. The infant in the previous case was described as being “well-hydrated.” What are some clues from the history and on physical exam that would reassure you of his hydration status?

2. In an infant with recurrent projectile vomiting secondary to pyloric stenosis, what might you expect to see on his serum chemistry panel, in particular his serum chloride, potassium, and bicarbonate?

Answers to Practice Questions:

1. On history, a well-hydrated infant would have a normal number of wet diapers (urine output), no recent weight loss, production of tears when crying, and normal activity and feeding. On exam, the well-hydrated infant would have a non-depressed anterior fontanel, moist mucous membranes, normal heart rate, blood pressure, and respirations, normal skin turgor, capillary refill time of <2 seconds, normal color, and strong pulses.

2. Pyloric stenosis classically causes a hypochloremic (low Cl⁻), hypokalemic (low K⁺) metabolic alkalosis from the associated loss of gastric acid from the stomach. However, the infant usually seeks medical treatment prior to the development of this metabolic derangement.
ICR Pediatric Issues: Small Group Case Studies

CASE 1:

You are a physician working in the Emergency Department and your first patient of the evening shift is a 3 week-old male whose mother and grandmother brought him in because of fever. At home he felt warm to the touch and had an axillary temperature of 38.8°C (101.8°F). The mother reports he has been "really sleepy" all day and not interested in feeding. She wonders if he might have caught her cold.

1. What do you see as the patient’s Chief Complaint?

2. What additional History of Present Illness would like to know, and why?

3. What relevant Past Medical and Family History or Review of Systems information would be useful to know?

4. What diagnoses are you considering at this time? (Differential Diagnosis)

The child is quiet, with minimal activity in his grandmother's arms. His eyes are open, but he does not track. Vital signs taken in the ED: Temp 39.8°C (103.6°F), HR 152/min, RR 50/min, and BP 80/64. His anterior fontanel is soft and flat. Conjunctivae are clear and he has normal red reflexes. Oropharynx is normal and tympanic membranes are clear and mobile. He is unable to support his head, but his neck is supple. Lungs are clear to auscultation and the cardiac exam is
unremarkable. The abdomen is soft and without organomegaly. Extremities are normal and the skin is without any apparent rash.

5. How do these physical exam findings change the diagnoses you are considering?

6. What laboratory or diagnostic tests are indicated in this child?

7. What is the probable diagnosis for this child?
CASE 2:

Your next patient of the day is a 9 month-old male brought in by his mother because he “won’t stop crying.” He seemed fine yesterday but was awake crying all night and today he is constantly fussy. She reports that if she puts him down “he just sits there and really screams and reaches for me.” About 4 weeks ago he was diagnosed with acute otitis media and treated with amoxicillin, but appeared to have gotten better except for a cold his mother thinks he caught in daycare. He felt warm this morning, but they do not have a functioning thermometer at home.

1. What do you see as the Chief Complaint?

2. What additional History of Present Illness do you want to know?

3. What relevant Past Medical and Family History, Social history, or Review of Systems information might be particularly useful?

4. What possible diagnoses are you considering at this time? (Differential Diagnosis)
The child is being held by his mother and appears irritable and fussy but is alert and watching you carefully. Vital signs taken in the ED: Length 71cm (50\textsuperscript{th} percentile), weight 8.2 kg (10\textsuperscript{th} percentile), HR 118/min, RR 28/min, Temp 99.3°F, BP 118/76 (child crying uncontrollably during measurement). He has clear nasal discharge, but his oropharynx is otherwise normal and tympanic membranes are clear and mobile. His neck is supple and several small (<1cm) anterior cervical lymph nodes are palpable. Lungs are clear to auscultation and cardiac exam is normal. Abdominal exam does not reveal obvious abnormalities but is difficult due to the child’s lack of cooperation. While performing his abdominal exam, you notice he does not appear to be moving his left leg and cries out when you attempt to manipulate it.

5. What else do you think is important on physical exam?

6. What laboratory or other diagnostic studies would your order, and why?

7. From the information available, what is the most likely diagnosis?
CASE 3:

You are asked to see an 18 year-old female who presents to the adolescent clinic in November with 4 days of dull, constant abdominal pain. The pain is located in both lower quadrants and it began shortly after her menses last month. She describes the pain as “crampy.” She also reports having intermittent fevers since her symptoms began. She has no history of past medical problems. She has smoked tobacco for the past 2 years but she states that she does not drink.

1. What do you see as the Chief Complaint?

2. What additional History of Present Illness do you want to know?

3. What relevant Past Medical and Family History, Social history, or Review of Systems information might be particularly useful?

Her physical exam reveals the following:

Vital signs: T=100.5°F BP=110/60 mm Hg HR=90/min RR=14/min

She is alert and in no acute distress. Her conjunctivae are clear and her sclerae are non-icteric. Her pupils are round and react appropriately to light. She does not have any lesions inside her mouth and her posterior oropharynx appears to without erythema or exudate. On cardiac exam, she has a normal rate and rhythm and you cannot detect any murmurs. Her pulmonary exam is also benign: lungs clear bilaterally without wheezes, rhonchi, or crackles. However, on her abdominal exam, she has mild left lower quadrant tenderness to light palpation. Her abdomen though is still soft, non-distended, with normative bowel sounds, and without cost vertebral angle tenderness. You cannot palpate a liver edge or an enlarged spleen.
4. What else do you think is important on physical exam?

5. What laboratory or other diagnostic studies would you order, and why?

6. Construct a problem list for this patient’s presentation.

7. Construct a prioritized differential diagnosis. What is your leading diagnosis?

8. How might you approach the management of this patient?
Patient 1:
A 45-year-old Air Force physician with no significant medical history presents for his periodic physical exam. He reports that he has been feeling progressively more tired over the past 4 to 6 months, having a harder time getting up for work in the morning, and sometimes requiring a nap when he gets home from work. His skin has also been quite dry, and his hair has been more brittle, without improvement despite trying different shampoos. He has not been eating more, but has gained about 10 pounds during this time. He just figures he is getting old, but his wife wanted to make sure he brought up the fatigue, because until the last 6 months he was always full of energy.

Questions:
1. What additional questions should you ask him?
2. What should you focus on in your physical exam?
3. What diagnostic tests should you perform?

Patient 2:
A 43-year-old woman complains of palpitations, heat intolerance, insomnia, and decreased menstrual flow over a period of 3 months. Her employer has become concerned because of a series of errors on tax preparation forms on which she has worked. She says the only good news is that over the past two months she is losing weight despite eating more than she has ever eaten in her life. Her mother and sister both have underactive thyroids and are taking levothyroxine therapy. She smokes ½ packs of cigarettes daily.

Questions:
1. What additional questions should you ask her
2. What should you focus on in your physical exam?
3. What diagnostic tests should you perform?

Learning Objectives
By the end of the session, the student should be able to:
1. Recognize the common symptoms and physical exam findings for hyperthyroidism and hypothyroidism.
2. Differentiate Graves' disease from other causes of hyperthyroidism.
3. Understand the basic pathophysiology of Graves' disease.
4. Identify common and/or distinctive history, physical examination and laboratory patterns for the following conditions: Graves’ disease, toxic multinodular goiter, toxic adenoma, subacute thyroiditis, surreptitious ingestion of thyroid hormone, pituitary TSH-secreting tumor, and subclinical hyperthyroidism
5. Recognize the clinical presentations of thyroid storm and myxedema coma

Overview:
This section of your syllabus will review common syndromes in medicine—hyperthyroidism and hypothyroidism. Emphasis will be placed on understanding pathophysiology as well as recognizing patterns of symptoms, findings, and laboratory tests in both hyperthyroidism and hypothyroidism. Further, key findings seen with several common causes of hyperthyroidism and hypothyroidism will be discussed.

Additional References:


Part 1: Hyperthyroidism

Introduction

It is helpful in thinking about the differential diagnosis of hyperthyroidism to consider the distinction between two terms, which are often used interchangeably: hyperthyroidism and thyrotoxicosis. Thyrotoxicosis is the most correct term for ALL causes of thyroid hormone excess; this syndrome can be caused by excessive production of thyroid hormones, excessive leakage of stored hormones from a damaged gland, or over-ingestion of exogenous thyroid hormones. The term hyperthyroidism implies excessive production of thyroid hormones by the thyroid gland--a single slice of the "pie" represented in the spectrum of thyrotoxicosis.

The Thyrotoxic Syndrome:

Many patients with overt hyperthyroidism will have multiple, but not all of the myriad consequences of physiologically excessive thyroid hormone. Virtually every organ system has the potential for manifestations.

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Increased sweating, Fine and &quot;limp&quot; hair texture, &quot;Velvety&quot; skin texture</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Wide pulse pressure, Tachycardia, Atrial fibrillation, High-output CHF, Thyrotoxic cardiomyopathy</td>
</tr>
<tr>
<td>Nervous/Psychiatric</td>
<td>Tremor, Impaired concentration, slowed thinking, Nervousness and anxiety, Irritability</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Hypomania, Depression, Insomnia</td>
</tr>
<tr>
<td>Muscular</td>
<td>Proximal weakness, Decreased endurance</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hyperdefecation, Nausea and vomiting, Weight loss</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Menstrual Irregularity, Decrease libido, Renal stones/hypercalciuria, polyuria</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypercalcemia/hypercalciuria, Infertility/Decreased libido</td>
</tr>
<tr>
<td>Skeletal</td>
<td>&quot;High turnover&quot; osteoporosis, Increased serum alkaline phosphatase</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Increased plasma volume, (result: apparent &quot;anemia&quot;, though RBC mass is normal)</td>
</tr>
</tbody>
</table>
Many symptoms of thyrotoxicosis are shared by common anxiety states. A clue to diagnosis is that in thyrotoxicosis, symptoms tend to be pervasive rather than situational. So, if patients feel nervous at night and rather constantly during the day under no externally stressful circumstances, it’s more likely for them to be thyrotoxic. Paroxysmal symptoms should make you doubt the presence of thyrotoxicosis.

**Physiology Worth Remembering:**

Like many endocrine systems, normal thyroid function is dependent on a physiologic "chain of command." The "headquarters" in the hypothalamus releases thyrotropin releasing hormone (TRH) via the hypophyseal portal system as a signal for specific anterior pituitary cells to release thyrotropin (TSH), which enters the venous effluent to communicate with the systemic circulation and ultimately with the thyroid follicular cells. Binding of TSH to a specific receptor on the follicular thyroid cell results in several key actions of the cell:

- Active iodide transport from the extracellular to the intracellular compartment
- Organification of iodide (incorporation into iodotyrosines)
- Coupling of iodotyrosines to form iodothyronines
- Synthesis of thyroglobulin
- Release of stored thyroid hormones from the gland into the circulation

**Checks and Balances:** Normally, the hypothalamus and anterior pituitary are exquisitely sensitive to feedback from circulating thyroid hormones. There is an individually determined "set point" for the release of TRH and TSH. Below "set point", TRH and TSH release are augmented, and their serum concentration is consequently increased. Above "set point", TRH and TSH release is profoundly inhibited, and the serum concentration of the "higher headquarters" hormones is thus low. The exquisitely sensitive nature of the relationship of serum T4 and T3, and TSH (and TRH, except that we don't clinically measure it), forms the basis for the interpretation of modern thyroid function tests.

Nature has provided us with another exquisitely sensitive means of regulating thyroid hormone effect in the body. Of the two thyroid hormones, triiodothyronine (T3) is by far the more potent. Normally, most T3 is derived intracellularly in peripheral tissues by the deiodination of thyroxine (T4), which acts as a reservoir. When thyroxine is present in excessive quantities in serum, peripheral tissues can down-regulate the deiodination process, and form less T3-and buffer against the thyrotoxic syndrome. This fact explains why patients who take excessive amounts of L-thyroxine usually don't develop severe symptoms. The other important caveat to derive here is that in states of hyperthyroidism, thyroidal production of T3 is abnormally augmented, thus potentiating the expression of symptoms.
Thyroid Function Testing Made As Easy As Possible

Serum Thyroid Hormone Tests

<table>
<thead>
<tr>
<th>TSH</th>
<th>T4</th>
<th>T3</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
<td>&quot;Subclinical&quot; Hypothyroidism</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>Normal or Low</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>&quot;Subclinical&quot; Thyrotoxicosis</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Normal or High</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>High</td>
<td>T3 Thyrotoxicosis</td>
</tr>
</tbody>
</table>

Notice that there are possibilities we haven't listed--they are uncommon, but important to recognize. If "the scene of the crime" is the pituitary or hypothalamus--not the thyroid--the TSH will be inappropriate for the measured T4 and/or T3. Thus, if the T4 and/or T3 is high AND the TSH is NOT LOW, you must suspect pituitary disease (TSH-dependent hyperthyroidism). Similarly, if the T4 is low AND the TSH is NOT HIGH, you must suspect pituitary disease (secondary hypothyroidism).

Radioactive Iodine Uptake (RAIU): A radioisotope (usually iodine-123 or iodine-131) is administered orally to the patient; the number of "counts" is measured prior to administration and then Geiger counter measurements are performed directly over the thyroid gland 4-6 and then 24 hours later. The number of counts over the thyroid divided by the number of counts administered represents the RAIU. Normal RAIU for euthyroid individuals is in the range of 10-30% at 24 hours. Patients with hyperthyroidism (overproduction of thyroid hormones) will have an increased RAIU, as long as the entire thyroid gland is involved in the disease process. Patients with thyrotoxicosis resulting from leakage or ingestion of thyroid hormone, on the other hand, will have a low RAIU. Once the syndrome of thyrotoxicosis is recognized clinically and confirmed by measurement of serum TSH and T4 and/or T3, RAIU is a valuable "next step." Naturally RAIU cannot be obtained in pregnant women or generally in women who are breastfeeding.

In addition to the measurement of RAIU, most patients with the thyrotoxic syndrome will benefit diagnostically from a thyroid scan. The thyroid scan shows where in the thyroid the uptake is occurring and may be diffuse, as in Graves' disease, or focal as with a solitary autonomously functioning thyroid nodule or multinodular goiter.

Thyroglobulin: Thyroglobulin is a protein produced only by follicular thyroid epithelial cells, and represents a storage matrix for thyroid hormones. A small quantity of thyroglobulin is measurable in the blood of normal individuals, and will be either normal or high in patients with true hyperthyroidism or thyroid hormone leakage. By contrast, it will be very low or undetectable in patients who have thyrotoxicosis due to ingestion of exogenous hormone.

Differential Diagnosis of Thyrotoxicosis:

The “Usual Suspects”

Graves' Disease (alias, diffuse toxic goiter): In any age group, Graves' disease is the most common form of thyrotoxicosis. In the young, the syndrome of thyrotoxicosis will be due to Graves' disease about 90% of the time; in the elderly, thyrotoxicosis will be due to Graves' disease about 65% of the time (toxic adenoma and toxic multinodular goiter comprise most of the balance). For this reason, we can approach the differential diagnosis of thyrotoxicosis as "rule out Graves' disease".
"Fingerprints at the Crime Scene"

- **Eye Signs:** Anyone with thyrotoxicosis can have physical examination findings of stare or lid lag (for that matter, anyone who’s anxious or scared can exhibit these findings!). But, only Graves’ disease will be associated with findings such as proptosis ("bug eyes"- remember the late comedian Marty Feldman as an extreme example), conjunctival erythema, and periorbital soft tissue swelling/lid edema, findings known collectively as Graves’ ophthalmopathy or orbitopathy.

- **Pretibial myxedema:** This is a brawny, usually erythematous dermal lesion found on the Anterior shins. It is uncommon (therefore not very sensitive), but very specific for Graves’ Disease in a thyrotoxic patient. Most patients with pretibial myxedema also have Graves’ ophthalmopathy.

- **Diffuse goiter:** Usually the thyroid is 2x or more the size of a normal thyroid, and without palpable nodules. You may be able to hear a bruit over the gland or over the supraclavicular fossae, reflecting increased blood flow to the hyperactive gland.

- **RAIU High:** With diffuse uptake pattern on scan.

- **Thyroid Antibodies:** Thyroid stimulating antibodies are the proximate cause of hyperthyroidism in Graves’ disease. Serum anti-thyroid peroxidase and anti-thyroglobulin antibodies are often detectable in Graves’ disease, postpartum thyroiditis, and most cases of painless thyroiditis, but they usually are not detectable in other forms of thyrotoxicosis.

**Pathophysiology:**

In Graves’ disease, the thyroid is victimized by an autoantibody to the TSH receptor, which stimulates the receptor. The thyroid responds as if to TSH by actively transporting iodide, organifying it coupling iodothyronines to form T4 and T3, and synthesizing thyroglobulin and releasing formed thyroid hormones.

Toxic Adenoma: Usually, toxic adenoma is associated with a large (> 3 cm) palpable solitary thyroid nodule. On thyroid scan, all radioiodine will concentrate within the palpable nodule, and the remainder of the gland will have decreased uptake. Specific markers of Graves’ disease, such as TSH-receptor antibodies will be absent.

Toxic Multinodular Goiter: These patients will have an irregular, lumpy-bumpy thyroid gland which may feel like a bag of marbles or birdshot. On thyroid scan, the radioiodine uptake pattern will be heterogeneous "hot and cold", corresponding with hyperfunctioning and hypofunctioning regions of the gland.

Destructive Thyroiditis: This suspect comes in three flavors--
- Postpartum thyroiditis (5-10% of all pregnancies; higher risk if it happened during a prior pregnancy): Typically, onsets within three months post-partum with mild thyrotoxic symptoms.
- Painful (subacute) thyroiditis (AKA Granulomatous thyroiditis, De Quervain’s thyroiditis). Characterized by exquisite tenderness of the thyroid on physical exam, often accompanied by sore throat or earache (as referred pain), fever, and night sweats.
- Painless (silent) thyroiditis: Characterized by a nontender thyroid, which may or may not be palpably enlarged; frequently accompanied by positive anti-thyroid peroxidase antibodies.

In each variety of thyroiditis, there are some generalizations, which can be clinically helpful:
- No eye signs (except the non-helpful stare and/or lid lag, maybe)
- RAIU very low
- Thyrotoxicosis self-limited, usually resolves within 12 weeks; often followed by hypothyroid phase lasting up to six months.
Pathophysiology of thyroiditis:

For whatever reason (viral toxicity; autoimmune damage; etc.), the thyroid follicular cells become damaged and/or die, and passively leak thyroid hormones, which have already been formed. Once the available supply of thyroid hormones has leaked out, new quantities can’t be formed because of the cellular damage-accounting for the hypothyroid phase of the illness.

Exogenous thyroid hormone ingestion (a.k.a. thyrotoxicosis factitia): We see this in everyday practice among patients who take thyroid hormones as treatment for hypothyroidism, thyroid nodules, or non-toxic goiter. The major key to diagnosis is clinical suspicion (patient on prescription thyroid hormone, or is a health worker concerned with weight or "slow metabolism"); confirmation is the identification of a very low or undetectable serum thyroglobulin, and a low RAIU.

TSH-dependent Hyperthyroidism: These forms of the thyrotoxic syndrome are collectively rare, but should be suspected when the patient has unequivocal signs of thyroid hormone excess along with elevated serum free thyroxine and/or T3 AND a serum TSH which is > 0.1 mU/L. The differential diagnosis of TSH-dependent hyperthyroidism includes the following entities:

- **Pituitary TSH-secreting adenoma:** An abnormally regulated clone of cells resists normal T4/T3 feedback control and hypersecretes TSH which cannot in turn be suppressed.

- **Pituitary/Hypothalamic T4/T3 resistance:** This is a genetic mutation of typically autosomal dominant inheritance, wherein there is central resistance to the normally suppressive effect of T4 and T3 feedback on TSH secretion, due to a mutation in the thyroid hormone receptor.

- **HCG-secreting neoplasms** (most notably choriocarcinoma and molar pregnancies): at very high serum concentration HCG itself can activate the TSH receptor, with the attendant consequence of inappropiate production of T4 and T3. Unlike the above disorders, TSH is < 0.1 mU/L in this disorder.

Treatment of Thyrotoxicosis

**Beta-blockers,** such as propranolol and atenolol, are extremely useful symptomatic treatment for thyrotoxicosis of ANY etiology. These agents can be dose-titrated as needed to control the resting pulse rate to < 80 beats per minute. Most patients report relief of nervousness, tremor, and insomnia, but it is important to realize that these drugs do not improve muscle weakness, heat intolerance, exertional fatigue, weight loss, or Graves' ophthalmopathy. **Antithyroid drugs of the thionamide** class include methimazole and propylthiouracil (PTU) and in the U.S., and can be used in the treatment of true hyperthyroidism (Graves' disease, toxic adenoma, and toxic multinodular goiter). Due to the enhanced risk of hepatic necrosis in patients taking PTU, the FDA and the American Thyroid Association have recommended that PTU usage be confined to the first trimester of pregnancy (during which time methimazole is not preferred due to a risk of embryopathy (aplasia cutis and choanal atresia). These drugs interfere with the organisation of iodide and the coupling of iodotyrosines. Approximately 5% of patients using these agents will develop medication intolerance within the first 3 months of treatment; common adverse reactions are rash and arthralgias, but approximately 0.5% of patients will develop chemical hepatitis or agranulocytosis. Monitoring for toxicity of thionamides can be especially problematic among active duty military patients and their families when the inevitable PCS move or deployment occurs, and this need should be considered when counseling these patients regarding treatment options. **Iodides,** such as SSKI or sodium ipodate, block release of pre-formed thyroid hormones and reduce vascularity of the thyroid gland over a period of two to four weeks of use. Indications for use of iodides include severe thyrotoxicosis (including thyroid storm) and preparation of patients with Graves' disease for thyroidectomy surgery. Iodides should never be given before antithyroid drugs are on board.
The most popular definitive treatment for Graves' disease in the military care setting (and throughout the U.S. at large) is oral administration of radioactive iodine. Advantages of this mode of therapy for military patients and providers include ease of administration; relative absence of serious adverse effects; and the typically one-time need for treatment, rendering long distance consultative care possible. Iodine-131 is incorporated into the thyroid gland thanks to the overactive iodine pump mechanism, and emits a lethal dose of radiation to affect cell kill localized to the thyroid, thanks to the avid concentration of the isotope by the gland. After single dose administration, most patients become hypothyroid over a period of two to three months. A few patients require a longer period of time to reach nadir T4 and T3 levels, and radioiodine treatment is traditionally considered a failure only if hyperthyroidism persists beyond six months post-treatment. Treatment failures can be re-treated with a higher dose of iodine-131. Major contraindications to radioactive iodine treatment include pregnancy (iodine will be taken up by fetal thyroid, with irradiation damage); nursing (iodine is secreted in breast milk, same result); and severe thyrotoxicosis (condition may transiently worsen, as radiation-damaged cells break down and "leak" pre-formed hormones into circulation). Graves’ ophthalmopathy may occur or worsen with increased frequency after radioiodine usage, hence severe ophthalmopathy is a contraindication for this modality as well.

Surgical thyroidectomy is a frequently used option for young patients with toxic adenoma or toxic multinodular goiter, and is generally reserved for very rare and difficult-to-manage Graves' disease or patients with active Graves’ ophthalmopathy, which may actually be aggravated by radioiodine. Outcomes of surgery in experienced hands approximates the success rate of radioactive iodine; however, risks of untoward reactions to anesthesia recurrent laryngeal nerve injury with persistent hoarseness and parathyroid gland injury with permanent hypoparathyroidism are unique to surgery. Considering the ease and convenience of radioactive iodine treatment, most patients and physicians prefer to avoid surgery except in specific and problematic circumstances.
### Part 2: Hypothyroidism

#### Signs and Symptoms

The trend of the past twenty years has been to diagnose hypothyroidism earlier and earlier in its natural history, before the patient evolves into a late-stage "poster child" presentation. A low threshold for serum testing in patients with suspected hypothyroidism is required due to the relatively subtle nature of signs and symptoms. Hypothyroidism is common, easily treatable, and prone to present with non-specific findings. If one considers hypothyroidism to be the "photographic negative" of hyperthyroidism, it is relatively easy to appreciate compatible findings which should trigger appropriate testing:

<table>
<thead>
<tr>
<th>Skin:</th>
<th>Dry skin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yellowish discoloration (due to carotene deposition)</td>
</tr>
<tr>
<td>Cardiovascular:</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Diastolic hypertension</td>
</tr>
<tr>
<td></td>
<td>Pericardial Effusion</td>
</tr>
<tr>
<td>Nervous:</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Sluggishness</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>Apathetic affect</td>
</tr>
<tr>
<td></td>
<td>Delayed return phase of deep tendon reflexes</td>
</tr>
<tr>
<td></td>
<td>Dementia or more subtle cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Psychosis (rare)</td>
</tr>
<tr>
<td>Muscular:</td>
<td>Stiffness and cramps</td>
</tr>
<tr>
<td></td>
<td>Elevated serum CK</td>
</tr>
<tr>
<td>Gastrointestinal:</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Hypomotility</td>
</tr>
<tr>
<td>Genitourinary:</td>
<td>Menstrual irregularity (menorrhagia common)</td>
</tr>
<tr>
<td></td>
<td>Decreased libido</td>
</tr>
<tr>
<td>Endocrine:</td>
<td>Decreased metabolic rate</td>
</tr>
<tr>
<td></td>
<td>Weight gain (usually &lt;20 pounds)</td>
</tr>
<tr>
<td></td>
<td>Cold intolerance</td>
</tr>
<tr>
<td></td>
<td>Goiter (usually firm texture)</td>
</tr>
<tr>
<td></td>
<td>Hypercholesterolemia (high LDL)</td>
</tr>
<tr>
<td>Hematologic:</td>
<td>Normocytic anemia</td>
</tr>
</tbody>
</table>

#### Etiology of Hypothyroidism

Upwards of 90% of the time, serum testing (see below) will confirm primary hypothyroidism as the underlying etiology. In the majority of adult-onset primary hypothyroidism cases, the cause will be autoimmune thyroid disease, a.k.a. chronic thyroiditis, a.k.a. Hashimoto's thyroiditis. The syndrome is, more likely to occur in patients with a family history of autoimmune thyroid disease (either chronic thyroiditis or Graves'), or who also have other autoimmune disease such as Type I diabetes, lupus, rheumatoid arthritis, immune thrombocytopenia, Sjogren's syndrome, pernicious anemia, myasthenia gravis, etc. Adults may manifest transient hypothyroidism lasting for months up to about one year during the course of painless or postpartum thyroiditis. Patients who have a history of thyroid surgery or radioactive iodine treatment may tend to develop thyroid failure precipitously at the time of
treatment. Worldwide outside of the U.S., there are still pockets of iodine deficiency, which is still the most common cause of hypothyroidism worldwide.

In unusual cases, hypothyroidism may result from inadequate production of bioactive TSH. This form of hypothyroidism is secondary hypothyroidism. It is important to recognize this syndrome, because it is unlikely to occur in isolated form. Most of the time, TSH deficiency exists parallel with deficiencies of other pituitary hormones such as growth hormone, ACTH, and gonadotropins. When one finds evidence of secondary hypothyroidism, a comprehensive testing of other pituitary hormone function is required.

**Biochemical Test Results**

Because signs and symptoms are non-specific, it is important to obtain serum TSH and free T4 whenever one has a low to intermediate suspicion of thyroid disease. Primary hypothyroidism, is confirmed by the finding of a serum TSH above the upper limit of the normal range (usually around 4.5 mU/L). A high TSH accompanied by low free T4 is characteristic of classic primary hypothyroidism; if the high TSH is accompanied by a normal-range free T4, the syndrome is said to be "subclinical" hypothyroidism. Secondary hypothyroidism is characterized by a frankly low free T4 combined with a serum TSH, which is either not elevated or which, is minimally elevated. The minimally elevated TSH is considered "inappropriate" in the setting of a severely depressed free T4; it often reflects immunoreactive TSH which has reduced bioactivity due to abnormal glycosylation (post-secretory modification).

<table>
<thead>
<tr>
<th>TSH</th>
<th>Free T4</th>
<th>T3</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated</td>
<td>Decreased</td>
<td>Normal or decreased</td>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
<td>&quot;Subclinical&quot; hypothyroidism</td>
</tr>
<tr>
<td>Normal/decreased</td>
<td>Decreased</td>
<td>Normal or decreased</td>
<td>Secondary hypothyroidism</td>
</tr>
</tbody>
</table>

**Thyroid function serum tests in hypothyroidism**

Treatment of hypothyroidism is comparatively simple, and all primary physicians should be comfortable prescribing and monitoring the adequacy of treatment. Simply stated, the goal of treatment is thyroxine replacement. For advanced thyroid failure in the elderly it is generally prudent to initiate therapy at a very low dose (on the order of 25 mcg levothyroxine daily), because in the hypothyroid state cellular thyroid hormone receptors are extraordinarily upregulated and patients will be profoundly sensitive to the effects of even ultra-low dose levothyroxine. Additionally, levothyroxine increases myocardial oxygen consumption and demand, which may precipitate unstable coronary syndromes in patients with active coronary heart disease. The dose of levothyroxine can be increased by 25 mcg every two to three weeks until full replacement is achieved For replacement most, patients will require on the order of 1.6 mcg per kg body weight of levothyroxine, daily. For most adults, this calculates to a daily dose of 100-200 mcg/day.

Serum TSH is generally the only necessary test for monitoring adequacy of therapy in patients with primary hypothyroidism, based upon the principle of negative hormonal feedback on the pituitary gland. It is generally recommended that the clinician allow 6-8 weeks between dose changes to permit establishment of steady-state TSH secretion before assessing adequacy of the levothyroxine dose. Certain medications increase dose requirement; these include estrogens (increased thyroxine binding globulin; decreased free T4), colestipol/cholestyramine (bind T4 in the gut reducing enterohepatic recycling), calcium supplements, sucralfate, and iron sulfate (all reduce thyroxine absorption from the gut), and sucralfate (decreased absorption).

Patients with secondary hypothyroidism require monitoring of free T4, rather than TSH, since by definition their secretory capacity for TSH is abnormal. A dose titrated to maintain a free T4 serum level within the normal range, along with careful assessment of symptoms and liberal application of clinical judgment is required.
Military-Specific Aspects of Thyroid Disease

Thyrotoxicosis is a military-relevant diagnosis, because Graves' disease is a common disease of young people. It is the prototype of a diagnosis with short-term impact on world-wide service and physical readiness, yet with a favorable long term prognosis provided treatment is timely and appropriate. When diagnosed with Graves' disease, military members should be placed on temporary profile (Army and Air Force) or Limited Duty (Navy and Marine Corps) for 90-180 days. Duty restrictions should include no deployments and no physical fitness testing or physically-demanding ordinary duties (may involve a "light duty only" prescription). Once the hyperthyroid state is controlled, duty restrictions can be liberalized at the discretion of the treating provider and the supervisor. It is often desirable for the physician to discuss the service member’s situation with the service member's supervisor. Hypothyroidism, whether naturally occurring or treatment-related, requires special provisions. Patients should not be expected to operate dangerous or heavy machinery while hypothyroid. Normal activity can generally be resumed after 30-60 days of levothyroxine replacement therapy. Medical Evaluation Boards for hyperthyroidism and hypothyroidism are normally required only if the members condition remains uncontrolled after one year of treatment (the expiration deadline for temporary profiles/Limited Duty).

Now back to our patients….

A. A 45-year-old Air Force physician who reports progressive fatigue with some weight gain, dry skin, and brittle hair.

1. What additional questions should you ask him?
At first glance, this patient’s presentation should make you think about hypothyroidism, as well as depression and a sleep disorder such as sleep apnea. Other useful questions to pose to him include: has he been more sensitive to cold temperatures, required extra blankets at night or warmer clothing than others or than he usually required previously? Has he fallen asleep at the wheel or while standing? Has his wife complained about loud snoring, frequent limb movements, or that he has stopped breathing or seemed to gasp for air while sleeping? Has he had difficulty concentrating, felt down or depressed, or felt guilty? If he has felt down or depressed, has it been to the point where he thought life was not worth living, or where he has considered taking his own life? How has his appetite been? What does he like to do for fun, and does he still enjoy those activities? Have others noted that he seems to be moving more slowly than usual? These questions address not only other symptoms that might suggest hypothyroidism, but also sleep apnea, periodic limb movements disorder (restless legs syndrome) and depression. Symptoms of sleep apnea or depression by no means rule out hypothyroidism, however, since both of these conditions can occur secondary to hypothyroidism, so it is critical to check a TSH level in a patient presenting with these findings.

2. What should you focus on in your physical exam?
The physical examination should, as always, begin with the vital signs; bradycardia and diastolic hypertension are characteristic of hypothyroidism, and with more advanced cases the respiratory rate, and temperature may all be depressed as well. The thyroid is frequently but not always enlarged in patients presenting with Hashimoto’s thyroiditis and the texture is described as firm or rubbery. For the remainder of the exam, the hair and skin should be carefully assessed. In particular, the eyebrows should be examined, with loss of hair on the lateral third of the eyebrows being more common with hypothyroidism (as well as syphilis). Comparison of the patient’s appearance to a prior photograph, such as their driver’s license, may be useful in this regard. Deep tendon reflexes are also important to carefully assess, since a delayed relaxation phase (return to the normal position after the initial contraction) is characteristic of hypothyroidism; the ankle jerk is often the easiest reflex with which to discern this pattern.

3. What diagnostic tests should you perform?
In addition to the TSH, free t4, complete blood counts should be obtained, since anemia is common with hypothyroidism, and a primary anemia is also in the differential for someone presenting with fatigue. The anemia is usually normocytic, but occasionally features a mild macrocytosis. A fasting lipid profile should be obtained as well, as hyperlipidemia is commonly associated with hypothyroidism. From what we are told, it appears that this individual
has significant, though not terribly severe, hypothyroidism. Upon confirmation, he should be started on levothyroxine, with the dose being titrated up as described above

**B. 43-year-old woman complains of palpitations, heat intolerance, insomnia, and decreased menstrual flow over a period of 3 months.**

1. **What additional questions would you ask?** Is she having any new eye symptoms such as redness, tearing, pain behind the eyes, or blurry vision. Is she having any neck pain? Has she been exposed to any exogenous iodine such as a CT scan with contrast? Is she experiencing heat intolerance or diaphoresis?

2. **What should you focus on in your physical exam?**
   On examination, does the patient have tachycardia or an increased systolic blood pressure and widened pulse pressure? You should closely evaluate her eyes. Is there conjunctival erythema or edema? Are the lids or periorbital areas swollen? Are her eyes protruding and are the extraocular muscle movements normal? Are her visual fields and visual acuity normal? Is her thyroid enlarged? Is it tender? Does it have an audible bruit? Are there thyroid nodules palpable? Does the patient have a murmur on cardiac examination? Is the skin moist, particularly in the palms? Does she have vitiligo? Is there a tremor? Are her deep tendon reflexes brisk?

3. **What diagnostic tests should you perform?**
   You should obtain a serum TSH value. If it is suppressed, you should measure free T4 and T3 values. If the patient has biochemical hyperthyroidism, you should obtain a nuclear medicine thyroid scan and radioactive iodine uptake (RAIU) test. If the diagnosis is in doubt or if the patient is pregnant (and therefore should not have nuclear medicine testing) then measurement of antibodies against the TSH-receptor may be helpful. If the patient has thyroid nodules palpable then a thyroid ultrasound should be obtained.

**Your next patient…thyroid disease in children**

You are evaluating a 10 year old female for obesity. She has had rapid weight gain in the past two years, despite seeing a nutritionist and being on a calorie-restricted diet. Her BMI is well above the 95% for her age. After plotting her growth, you determine that she has only grown 3 cm per year in the past two years and has gone from the 50% for height to the 5%. She continues to do well in school, although she does complain that she is always cold. Her mother has a history of hypothyroidism and is interested in having her daughter tested as well.

As in adults, pediatric thyroid disease most commonly leads to hypothyroidism or hyperthyroidism. Thyroid hormone, or thyroxine, regulates metabolism as well as multiple developmental genes. Neural development, in particular, is dependent on adequate levels of thyroid hormone. Untreated hypothyroidism in the first year of life results in permanent mental retardation. In addition, the rate at which children gain weight, grow linearly, and progress through puberty, are closely linked to the levels of thyroxine.

Congenital hypothyroidism occurs in 1 in 4,000 newborns and is most commonly caused by thyroid dysgenesis. The specific pathogenesis of thyroid dysgenesis is unclear. Universal screening for congenital hypothyroidism was introduced in the 1970s. Screening has successfully detected hypothyroidism during infancy, allowing treatment and preventing mental retardation. In addition, newborns with some congenital syndromes, such as septo-optic dysplasia, or other midline defects, such as a cleft palate or cardiac anomalies are at risk for thyroid-stimulating hormone (TSH) deficiency. On exam, these infants can have large fontanelles, lethargy, constipation, hypotonia, hypothermia, and excessive jaundice.

Newborns can also experience hyperthyroidism. In mothers with Grave’s disease, transmission of thyroid-stimulating immunoglobulins (TSI) across the placenta can cause neonatal thyrotoxicosis. With a few exceptions, hyperthyroidism in childhood is due to autoimmune disease. Graves disease in children has a peak incidence in the 11-15 year-old with a 5 : 1 female to male ratio.

In school-age children, the prevalence of acquired hypothyroidism ranges from 1 in 500 to 1 in 100 and is most often caused by chronic lymphocytic thyroiditis. In addition, some genetic conditions, such as Trisomy 21 and Turner syndrome have a high incidence of thyroid dysfunction. CNS neoplasms, particularly craniopharyngioma, as
well as cranial irradiation for children with acute lymphocytic leukemia are also at risk for TSH deficiency. Children with celiac disease or diabetes are at higher risk of hypothyroidism as well.

Monitoring growth and development is an important screening tool for thyroid disease in children. Physical exam findings are similar for adults and children with both hypo and hyperthyroidism. However, since pediatric patients develop and grow rapidly, changes in linear growth and cognitive or behavioral decline should prompt an evaluation that would include screening for thyroid disorders. Children who are overweight and short should be screening for hypothyroidism.

Finally, as with other pediatric disorders, normal values for serum thyroid function tests vary with age.

Although most children with obesity have exogenous causes for being overweight, most often excessive caloric intake, children who do not sustain a normal rate of linear growth (at least 4 cm per year), are likely to have an endocrinologic abnormality. You decide to order several tests for your patient, including thyroid function studies which reveal a significantly elevated TSH and a low free T4. She is started on synthroid, an oral thyroxine replacement, and increases her height up to the 40% and achieves a BMI in the 80% over the next 18 months.
Practice questions (and answers)
2-3 additional practice questions and answers, ok?

1. Which of the following findings would be expected in secondary hypothyroidism?
   a. TSH normal, FT4 decreased, T3 low or low-normal
   b. TSH decreased, FT4 normal, T3 normal
   c. TSH normal, FT4 increased, T3 normal
   d. TSH decreased, FT4 increased, T3 increased
   e. None of the above

2. A 50 year old nurse presents with unintentional weight loss, diarrhea and a new tremor. If you suspected a diagnosis of Graves’ disease and you found that she had a low RAIU, this diagnosis becomes?
   a. Much more likely
   b. Much less likely
   c. Neither much more or less likely

3. A newborn infant, who was born to a mother with Graves disease, is exhibiting symptoms of thyrotoxicosis. All of the following symptoms would be observed except:
   a. Irritability
   b. Macrosomia
   c. Tachycardia
   d. Goiter

4. A 33-year-old woman presents with severe anterior neck pain radiating to the left ear, nervousness and palpitations. She is afebrile. Her pulse is 104 beats per minute and her thyroid is exquisitely tender to palpation, mildly enlarged without nodules. Thyroid labs confirm an elevated free T4 and an undetectable serum TSH. Which of the following is the most likely cause of this patient’s presentation?
   a. Graves’ disease
   b. Surreptitious thyroid hormone usage
   c. Subacute thyroiditis
   d. Acute thyroiditis

5. A 28-year-old pharmacy technician presents with thyrotoxicosis. Which of the following labs would be most useful in showing surreptitious use of thyroid hormone?
   a. Suppressed serum TSH
   b. Elevated T3 but not T4 level
   c. Undetectable serum thyroglobulin
   d. A low radioactive iodine uptake at 24 hours
Answers:
1. A—TSH can be normal or decreased, FT4 is decreased and T3 can be normal or decreased in secondary hypothyroidism.

2. The answer is B much less likely. In Graves’ disease the RAIU should be increased (and in a diffuse pattern). The low RAIU suggests ingestion or leakage (i.e. thyroiditis) of thyroid hormone.

3. B—Microsoma is more common, not macrosomia

4. C—this is most consistent with subacute thyroiditis. Acute thyroiditis is an infectious process and presents with fever, fluctuance over the thyroid, and leukocytosis.

5. C—an undetectable serum thyroglobulin level is the most specific finding for surreptitious use of thyroid hormone. The other choices may occur with surreptitious use of thyroid hormone but can occur for other etiologies as well.
ICR Thyroid Case Studies

Case 1:

A 27-year-old female soldier is referred to your office by the Troop Medical Clinic. She serves in combat communications, and had received outstanding evaluations over her first two years of enlistment. However, over the last three months, her Sergeant noted her being so irritable that the performance of herself and her unit has greatly decreased. Although she had easily passed all her previous Physical Training tests, she failed her most recent test because she could do only six push-ups. On further questioning you learn that she has developed unexplained anxiety and difficulty sleeping and her menses have become more scant and irregular. At her weigh-in for the recent PT test, she was ten pounds lighter than six months ago. Sometimes, when sitting at her computer console, she feels her heart racing. The patient relates that her handwriting has been "slightly shaky" and she has noticed that her eyes have felt "gritty" for the last three weeks.

Question #1: With these initial complaints, what are the possible causes of this soldier's altered performance? Use the pneumonic INDICATE to consider broad disease categories and list possible specific disorders in each category applicable to this case that are consistent with the current information you have.

I --Infectious
N—Neoplastic
   --Neuropsychiatric
D--Degenerative (connective tissue disease)
I --Inherited (metabolic)
C-- Circulatory
A--Anatomic
T--Traumatic
E--Exogenous

Question #2: At this point, the differential diagnosis is quite broad, but a careful history will help to identify the cause of this problem. For each disorder listed in response to Question 1, what are specific questions on history that will help narrow the differential diagnosis?

Additional History:
Upon questioning, she tells you the following:
She has been totally healthy until the current problems began. Her husband has complained recently that the air conditioner in their apartment was set too cold. She has never been pregnant. Her only medication is a low-estrogen and progesterone combination birth control pill. Her last menstrual period was two weeks ago, and it was one day shorter than usual. When she visited the gynecologist six months ago, she had a normal physical examination and laboratory testing showed a normal blood count, chemistry profiles, and HIV screen. She also recently noticed that her collar feels tighter that she remembers it in the past.

Question #3: What can you conclude from this additional information? What information helps to support or refute each of the possible diagnoses outlined in question #1?

You now perform a physical examination of your patient.

Question #4: For each of your leading diagnoses at this point, list all pertinent physical findings that you would include in your evaluation of this patient.

The patient is a thin, slightly disheveled woman. Temperature is 98.4, blood pressure is 147/74 and her pulse is 104. Her skin is warm and her palms are moist. There is no evidence of Graves’ dermopathy or vitiligo. She has state and lid lag. She has scleral injection but no chemosis or proptosis, and her extraocular muscle movements are normal. Her thyroid gland is nontender, but it is diffusely enlarged to twice the normal size, with an audible bruit. She has no adenopathy. Her lungs are clear. She has a I/VI systolic ejection murmur heard best at the left lower sternal border and radiating to the aortic area. The examination of her abdomen is benign, with no masses or organomegaly. Breast and pelvic exams are normal. She has brisk deep tendon reflexes throughout but there is no clonus. She has a fine tremor of her hands and no lower extremity edema.

Question #5: At this point, how has your physical exam helped to prioritize your differential diagnosis? What is the leading diagnosis at this point?

Question #6: What initial laboratory tests would you order? Which ones are helpful if negative and tend to exclude possible diagnoses? Which ones are helpful if positive and tend to support possible diagnoses?
The patient's hematocrit is 38%, serum glucose is 100 mg/dL, "HIV" is negative, and hCG-beta is negative. Her chemistry panel reveals a serum calcium of 10.4 mg/dL, but is otherwise normal. Her free T4 is 67.5 pmol/L (normal 10.3-30.6) and her TSH is 0.01 mIU/L (normal: 0.51-4.90). Antithyroglobulin antibody was negative, but thyroid peroxidase antibody is strongly positive at 250 (nl<2.0). Thyrotropin binding inhibitory immunoglobulin (TBII) activity was 22% (normal: <10%). Her thyroid stimulating immunoglobulin (TSI) level was 155% (normal <130%). The patient's 24-hour radioiodine uptake was 58.9% (normal: 8-30%) and thyroid scan shows this uptake to be diffuse.

**Question #7:** What does each of these laboratory tests tell you? What is the diagnosis in this patient?

**Question #8:** To this point, we have been considering the causes of thyrotoxicosis. What are the effects? List how each of the below organ systems that can be affected and specify how you would

- CNS
- Cardiac
- Respiratory
- Gastrointestinal
- Reproductive
- Dermatologic
- Urinary
- Musculoskeletal

**Question #9:** Graves’ ophthalmopathy, Graves’ dermopathy (pretibial myxedema), and thyroid acropachy can all be seen in patients with Graves’ disease. Which is the most and which the least common? Discuss current theories on the pathogenesis of these manifestations.

**Question #10:**
What forms of therapy are available for patients with Graves’ disease? What are the pros and cons of each approach?

After discussing treatment options, your patient has elected to receive a projected one year course of antithyroid drugs. You place her on atenolol 50 mg daily and methimazole 20 mg daily.
She returns in three weeks, reporting that she is already feeling much less jittery, that she is sleeping better and that her supervisor told her that her work was "getting back to normal."

**Question #11:** What are the major and minor adverse effects of antithyroid drugs?

**Question #12:** What further follow-up examinations and testing are necessary for this patient?
Case 2:

32 year old active duty Army CPT presents to your clinic with a three year history of cold intolerance, generalized fatigue, muscle cramping, skin dryness, paresthesias in his hands, forgetfulness, hypersomnolence, constipation, difficulty maintaining Army weight standards. He has noticed an increase in his collar size from 15 to 16, and his wife complains that his snoring wakes her up at night. His past medical history is significant for carpal tunnel syndrome requiring surgery. He is taking no medications. He is a non-smoker and rarely drinks since he finds recently that alcohol "puts him to sleep." Family history for Type 1 diabetes (younger brother) and hypothyroidism following “radioactive treatments” (mother).

Physical examination reveals a BP 117/86, pulse 68. His weight is 145# and he is 63.5 inches tall. Eye exam is normal. Neck exam reveals a thyroid that is easily visible with swallowing, firm in texture without nodules or bruit, and approximately twice-normal size. Skin exam reveals dryness, with scaling between the fingers, and hair exam is significant for graying at the temples. Achilles deep tendon reflexes while kneeling on a chair shows a greatly prolonged relaxation phase.

Initial Questions:

1. There are 15 clues to the diagnosis in his history and 7 supportive findings on his physical examination. What are they? Which of these is specific for the suspected diagnosis?
2. You have just received ordering privileges at your hospital. You review all the possible labs and radiology tests having anything to do with the thyroid. Explain why each of the following would or would not be helpful:

- Free T4
- Free T3
- TSH
- Thyroid peroxidase antibodies
- Thyroglobulin
- Thyroglobulin antibodies
- Chem-20
- CBC
- Lipid panel
- Thyroid ultrasound
- Thyroid scan
- Thyroid uptake of I-131 (RAIU)

The following laboratory data comes back to you within one week: CBC: Hct 36.2, MCV 98.4, RDW 13.2; Serum sodium 134, Creat 1.6, total cholesterol 265, free T4 < 4.0 pmol/L (normal 10.6-30.1), TSH 88.0 mIU/L (normal 0.51-4.9), anti-TPO 245 IU/mL (normal < 2.0).
Follow-up questions:

1. What is the diagnosis?

2. What is the most common cause of hypothyroidism in the United States? Worldwide?

3. Does his anemia require further evaluation?

4. Does his elevated serum creatinine require further testing?

5. How would you approach the elevated cholesterol?

6. State specifically how you would treat this patient's thyroid condition.

7. What advice would give him about driving or taking medications that make him drowsy?

8. How long should the patient be given before he is expected to meet military weight standards?

The patient is started on levothyroxine 0.1 mg daily. Two weeks later he presents to the emergency room with nausea, malaise, and orthostasis. On examination he is noted to have a SBP of 95/60 and a pulse of 110 BPM. Serum cortisol is measured at 1.8 ug/dL and goes to 7.2 ug/dL with synthetic ACTH injection.

Last Questions:

1. How do you explain his acute presentation?

2. What other endocrine diseases occur with increased frequency in men and women with autoimmune thyroid disease?
ICR: Polyuria and Diabetes Mellitus

Robert A. Vigersky, MD

Your first patient:
A 41-year-old woman is brought to the emergency room a one-month history of fatigue, blurred vision, polyphagia, polydipsia and polyuria. She has also noted a pruritic rash of her face and extremities. Her past history is notable for hypertension, hyperlipidemia, and migraine headaches. Her medications are propanolol and acetaminophen. Physical exam reveals that her blood pressure is 160/95, pulse rate 105 per minute, and respirations 22 per minute. Her weight is 165 pound and BMI 27. Physical examination shows no abdominal tenderness but the liver is palpable 5 cm below the right costal margin. There is no palpable spleen tip. There are eruptive xanthomas on her face, arms, and legs. The remainder of her examination is normal.

Laboratory results:

Serum chemistries: Arterial blood gas
Na 128 mEq/L pH=7.28
K 4.4 mEq/L pCO2=25mmHg
CO2 15 mEq/L pO2=142mmHg
Chloride 101 mEq/L
BUN 48 mg/dL
Creatinine 1.9 mg/dL
Calcium 10.1 mg/dL
Glucose 440 mg/dL
Serum Acetoacetic acid Positive
BUN 35 mg/dL
Serum ALT 125 U/L
Serum amylase <30 U/L

Objectives:
At the end of this session, students will be able to:
1. List the differential diagnosis of polyuria and understand how to use laboratory tests to confirm the diagnosis
2. Differentiate Type 1 from Type 2 Diabetes Mellitus in terms of pathophysiology, clinical, and laboratory features
3. Understand how to establish the diagnosis of diabetes mellitus and diabetes insipidus
4. List the macrovascular and microvascular complications to include how to prevent these complications
5. List the differential diagnosis of hypoglycemia and patterns of laboratory tests (i.e. insulin and C peptide patterns) for the “usual suspects”
6. Understand the pathophysiology and treatment guidelines for complications of diabetes mellitus
Questions about your first patient:
1. What other questions do you need to ask her?
2. What else should you look for on physical exam?
3. Construct a problem list
4. Do you need to order other tests?
5. What treatment is the most appropriate for her?

Problem List
1. Polyuria
2. Pruritic rash
3. Hepatomegaly and transaminasemia
4. Hyperpnea
5. Metabolic acidosis
6. Hyponatremia
7. Azotemia

Questions:
1. What is the most likely cause of this patient’s polyuria?
   a. Central diabetes Insipidus
   b. Diabetes Mellitus
   c. Compulsive water drinking
   d. Neurogenic bladder
   e. Acute glomerulonephritis

2. What is the cause of this patient’s acidosis?
   a. Lactate
   b. Acetoacetate (ketoacidosis)
   c. Glucose
   d. CO2
   e. Linoleic acid

3. Which of the following antibodies is likely to be positive in this patient’s serum?
   a. Anti-Jo antibodies
   b. Anti-nuclear antibodies (ANA)
   c. Glutamic acid decarboxylase (GAD)
   d. Islet cell antibodies (ICA)
   e. None of the above
4. What is the cause of this patient’s rash?
   a. Tinea cruris
   b. Lyme disease
   c. Acanthosis nigricans
   d. Hypertriglyceridemia
   e. Rubeola

**Answers:**
1. B
   The patient has hyperglycemia which exceeds the urinary threshold for glucose causing an osmotic diuresis. Diabetes Insipidus (central) is caused by a deficient in anti-diuretic hormone (vasopressin) and is not associated with hyperglycemia and would cause hyper- not hyponatremia. Compulsive water drinking and acute glomerulonephritis both have normal glucose levels.

2. B
   The patient has a metabolic acidosis which results from the accumulation of ketone bodies such as acetoacetate and beta-hydroxybutyrate that are derived from the free fatty acids that are secreted by adipocytes. CO2 is appropriately lower than normal in an attempt to compensate for the acidosis with a respiratory alkalosis. Respiratory acidosis causes an elevated of CO2. Glucose and lionoleic acid do not directly cause acidosis.

3. E
   The patient most likely has Type 2 diabetes. She is overweight, has eruptive xanthomas due to hypertriglyceridemia, and mild ketoacidosis. GAD and ICA antibodies are typical of Type 1 diabetes. Anti-Jo and ANA are not typical of patients with Type 1 or Type 2 diabetes.

4. D
   Eruptive xanthomas are pruritic papillary lesions on the face and trunk. Acanthosis nigricans appears as a velvety darkening of the skin in the skin folds, axillae, and back of the neck. Lyme disease typically begins with a single target lesion at the site of the tick bite. Tinea cruris is a scaly hyperkeratotic rash which typically appears in well-demarcated patches in interiginous regions. Rubeola (measles) is associated with a febrile illness with fever and cough preceding the development of a maculopapular and is usually seen in children.

**Your next patient….**
While stationed in Afghanistan, a 39-year-old Army National Guard soldier presents to his troop medical clinic with a two month history of increased urinary frequency, having to get up several times during the night to urinate and having his need to urinate interfere with his patrol duties. He also has had blurred vision over the past month, initially attributing it to the wind picking up sand or dust, but acknowledging that it seems to be a problem even when he has not been outside.
Questions:
1. What other questions should you ask?
2. What should you check on physical exam?
3. What laboratory testing should you obtain?
4. Construct a problem list
5. What causes of his polyuria and blurred vision should you consider?
5. Should he be evacuated from Afghanistan?

Overview:
This section of your syllabus will provide a rationale approach to the diagnosis of polyuria; particular attention will be paid to how to establish the diagnosis of diabetes mellitus and its complications, given the burden of this disease on society.
Pathophysiology and key findings which help establish the diagnosis will be stressed.
Cardinal Symptom: Polyuria

Polyuria potentially represents significant pathology, or, alternatively, it may simply reflect the personal habits of the patient. The first task facing the clinician when the patient complains of frequent urination is to establish whether or not the daily voided volume of urine is in excess of normal, or, alternatively, whether the patient has frequent voiding of small urine volume. In either case, patients may not accurately recall how often they have to void during the ordinary day, but they will know if they have to frequently excuse themselves from class or meetings. Usually, however, patients will more accurately recall how many times per night they wake up to urinate. Five or more episodes of nocturia per night are not uncommon in patients with polyuria.

**Point of Discrimination**: Increased daily volume of urine defines true polyuria. Based on the required daily waste solute excretion requirements, the normal volume of urine per day ranges from about 500 ml (at a maximally concentrated osmolality of > 1000 mOsm/kg) to about 2000 ml (at a urine osmolality of around 150 mOsm/kg). Most authors define true polyuria as a 24 hour urine volume in excess of 2,500 ml. Thus, to define the syndrome accurately, a cost-effective screening test is simply to measure the 24 hour urine volume! If the urine volume is normal, attention should be directed towards disorders of increased bladder irritability (cystitis, urethritis, spastic neurogenic bladder) or an overfilled bladder with incomplete emptying (sensory neurogenic bladder with "overflow") and, most often, prostatism in older men.

True Polyuria: Differential Diagnosis

Pragmatically, the next step in diagnosis after defining the syndrome correctly is to identify whether or not there is an abnormally high amount of solute to be excreted in the urine on a daily basis: that is to say, is there an osmotic diuresis? Since it is impossible to excrete pure solute in the absence of water, increased solute loads obligate increased renal water excretion. The most common cause of osmotic diuresis is diabetes mellitus. As the serum glucose level rises above the maximal concentration from which 100% of the filtered load of glucose can be reabsorbed from the glomerular filtrate (about 180 mg/dl – higher in the elderly), glucose begins to "spill" in the urine, obligating increasing renal water excretion to "wash" it out. This explains the cardinal symptom of polyuria in uncontrolled diabetes. The response to increased renal water loss is a slight (to extreme) decrement in ECF volume, and a slight (to extreme) increment in serum osmolality: both the volume and the osmolar signal stimulate vasopressin (which in this setting is largely ineffective) and also stimulate the hypothalamic thirst center: resulting in the cardinal symptom of increased thirst.

When the patient complains of frequent urination, it is always appropriate to do a urine dipstick for glucose! Common things being common, once you exclude "urologic" causes of frequent urination (i.e., the non-polyuric causes), the most likely explanation is diabetes mellitus. If the dipstick is positive, you have your diagnosis and it remains only to establish the severity and acuity of illness. If the dipstick is negative, and the urine volume is abnormally high, you must be dealing with one of the forms of the "other" diabetes, diabetes insipidus (DI), which comes in three flavors: 1) central DI due to deficient vasopressin release in response to increasing serum osmolality; 2) nephrogenic DI due to subnormal renal responsiveness to vasopressin (i.e., vasopressin resistance); and 3) dipsogenic DI, due to oral water intake sufficient to lower serum osmolality below

27:5
the threshold for vasopressin release. We will not further consider the DI syndromes at this time, but "tuck away" these ideas for future reference: 1) Central DI is an important clue to the diagnosis of an underlying pituitary or hypothalamic disorder; and 2) Nephrogenic DI is commonly associated with renal tubular diseases, and in reversible form, is commonly due to hypokalemia and hypercalcemia (this is a classic Internal Medicine pimp question!). Nephrogenic DI may also be due to a medication such as lithium (often prescribed for bipolar disorders). In the first two disorders, serum sodium and osmolality tend to be normal to slightly supernormal, while dipsogenic DI is characterized by very slight hyponatremia and hypoosmolality.

### Diabetes Mellitus: Diagnosis

The presence of symptoms of diabetes mellitus (polyuria, polydipsia, weight loss, hyperphagia, blurry vision) and significant glycosuria virtually cinches the diagnosis, but confirmatory testing depends on the corresponding serum glucose. Criteria for diagnosis as of January 2010 are as follows:

- Fasting glucose $\geq 126$ mg/dl
- Hemoglobin A1C $> 6.5$
- 2-hour post-75 gram glucose load $> 200$ mg/dl
- Random glucose $> 200$ mg/dl, with symptoms of DM (polyuria, polydipsia, and/or blurry vision)

In the absence of symptoms, the diagnostic thresholds should be met on at least two tests either at the same time or on two occasions when the patient is free of major transient physiologic stress (such as MI, sepsis, major trauma, or post-op from a major procedure). The reason for lowering the diagnostic threshold for diabetes from the prior 140 mg/dl to 126 mg/dl in 1997 is the observation that when subjected to oral glucose tolerance testing, the vast majority of patients with a fasting glucose $> 125$ mg/dl will exceed 200 mg/dl in the postprandial state. In addition patients with blood sugars in this intermediate range often have signs of early diabetic complications. The inclusion of A1C as a diagnostic criteria in 2010 resulted from the development of a worldwide standard for A1C, its low interassay coefficient of variation, the observation that complications are already present in those with an A1C over 6.5%, and the convenience of obtaining it because it can be obtained in the non-fasting state. The intent of the newer criteria is to minimize use of oral glucose tolerance testing, which has a high interassay coefficient of variation, usually adds expense and inconvenience to a workup at negligible clinical benefit.

### Classification of Diabetes

There are approximately 29 million people in the United States with Diabetes Mellitus (8.3% of the population) and 7 million of these have yet to be diagnosed and treated. Prevalent types of diabetes are officially known, cleverly enough, as Type 1 and Type 2 DM. These are separated on the basis of pathophysiology and response to treatment,
although in clinical practice, the division between the two is often muddy. Defining characteristics of these syndromes are summarized as follows:

**Type 1 DM**
- **Genetics:** Complex interaction between HLA haplotypes conveying risk + environmental triggers; roughly 50% concordance rate among identical twins; increased risk for sibs (6-10% vs. 0.4% in the general population)
- **Etiology:** autoimmune destruction of pancreatic islet beta cells
- **Markers:** islet cell and GAD (glutamic acid decarboxylase) antibodies; low endogenous insulin as measured by absent C-peptide response to physiologic stimuli (feeding, intravenous glucose, glucagon). C-peptide is the connecting peptide that links the A and B chains of pro-insulin. It can be measured in the serum of patients who have taken insulin and/or have antibodies to insulin because insulin does not cross-react in the C-peptide assay
- **Endogenous insulin reserve effectively absent**
- **Physiologic consequences:** Untreated, patients will experience ketosis even in the fed state, and can develop ketoacidosis when confronted with mild physiologic stress (such as an acute viral illness). The ketones are metabolites of free fatty acids which are released from fat cells in the absence of insulin
- **Insulin REPLACEMENT therapy is the only treatment option** (pancreas transplant is possible but not done in newly diagnosed patients and islet cell transplantation and immunotherapy are still experimental)

**Clinical Clues to Diagnosis:**
- Patients tend to be < 35 or > 65 years old at onset but it can occur at any age
- Untreated patients tend to have positive urine ketones (normally, a marker of a prolonged fast) in the postprandial state
- Patients tend to be at or below ideal body weight at the time of diagnosis
- Overall, Type 1 DM represents about 10% of all patients with Diabetes Mellitus

**Type 2 DM**

**Multiple factors contribute to the etiology of Type 2 diabetes. These include:**
- **Genetics:** Complex polygenic, non-HLA linked pattern usually (unusual forms may involve specific mutations in insulin gene or insulin receptor); typically strong family history among 1st degree relatives (13% vs. 5% in the general population); >90% concordance among identical twins.
- **Etiology:** Complex, variable spectrum of impaired insulin sensitivity at the level of hepatic, muscle, and fat tissue (INSULIN RESISTANCE) plus RELATIVE (but not absolute) insulin deficiency
- **Markers:** Absence of serum islet cell and GAD antibodies; measurable endogenous insulin response to physiologic stimuli (C-peptide ranges from detectable, but inappropriately low, to markedly elevated)
- **Endogenous insulin reserve limited but present**
- **Diminished secretion of GLP-1 (Glucagon-like peptide 1) which is made in the L-cells of the intestine and under normal circumstances stimulates insulin, reduces glucagon, delays gastric emptying, and reduces appetite**
- Decreased sensitivity of the beta cells to GLP-1 action which can be overcome with improved glycemic control
- Physiologic consequences: Untreated, patients may exhibit symptomatic diabetes, but will not have ketosis in the postprandial state. *Patients may develop ketoacidosis during extreme physiologic stress (MI, sepsis, stroke, major trauma, etc.), but will resist ketosis during minor illnesses*
- About 90% of the diabetics in the U.S. have Type 2 DM.

- Treatment options are diverse but always start with lifestyle modifications, i.e. diet and exercise. The pharmacologic options target the pathophysiologic factors shown above. These can include one or more of the following:
  - Oral hypoglycemic drugs:
    a. Metformin (decreases hepatic gluconeogenesis, and enhances peripheral tissue insulin sensitivity. Does NOT produce hypoglycemia when used as monotherapy)
    b. Insulin secretagogues:
      i. Sulfonylureas - such as glimepiride, glipizide and glyburide (stimulate endogenous insulin release in response to hyperglycemic signaling)
      ii. Non-sulfonylurea insulin secretagogues - such as repaglinide and nateglinide
    c. Thiazolidinediones, such as pioglitazone (enhances peripheral tissue insulin sensitivity. Does NOT produce hypoglycemia when used as monotherapy)
    d. DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin) which prevent the enzymatic destruction of endogenous GLP-1 by dipeptidyl peptidase-4 (DPP-4) and have some of the same effects as GLP-1 analogues
e. **SGLT-2 inhibitors**, such as canagliflozin and empagliflozin which are newly approved class of agents that lower the renal threshold for glucose thereby promoting glycosuria

- Injectable hypoglycemic drugs:
  a. **GLP-1 (glucagon like peptide-1) analogues** (e.g. exenatide and liraglutide) which stimulate insulin, reduce glucagon, delay gastric emptying, and reduce appetite
  b. **Insulin** (recombinant human or analog) (Figure)
    i. injectable analog insulins which comes in rapid-acting forms that peak in 1-2 hours (insulin aspart, insulin lispro, and insulin glulisine) and basal insulin without a peak (insulin glargine and insulin detemir)
    ii. injectable human (non-analog) insulin – “regular” insulin which is short-acting (peaks in 4 hours)
    iii. injectable intermediate-acting insulin – NPH insulin which peaks in 6-8 hours.

An inhaled insulin was approved by the FDA in 2014. It very rapidly acting with a peak effect within 30 minutes.

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**Chronic Complications of Diabetes**

Both Type 1 and Type 2 DM convey similar risk for the chronic microvascular complications of the disease. There is now incontrovertible evidence that both the duration and the severity of hyperglycemia increase the risk that these complications will appear in a given diabetic patient. Of equal importance, there is clear evidence from two large randomized, prospective studies (the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study) that the risk of diabetic complications is reduced by 25% for every 1% improvement in the hemoglobin A1C (see below). (Each 1% reduction of A1C represents about a 30 mg/dl of decrease in plasma glucose). Objectively, mean glycemia is best assessed by the measurement of the percentage of
hemoglobin A1C in the blood, quarterly. Hemoglobin A1C represents the irreversibly non-enzymatically glycosylated fraction of hemoglobin, which is determined by the availability of glucose in circulation. An A1c value close to normal portends excellent glycemic control. Another marker of glycemic control is fructosamine (glycosylated albumin) which reflects mean glucose for the previous 2 –3 weeks. This is a useful test in patients with hemoglobinopathies, in those with severe anemia, and in pregnant women or other patients in whom more frequent monitoring is necessary.

Molecular basis of diabetic complications: Many of the recognized long-term complications of diabetes can be related to non-enzymatic glycation of basement membrane and connective tissue peptides. Non-enzymatic glycation of basement membrane proteins tends to result in altered tertiary structure of the peptide; if it happens to be a receptor or ligand portion of a molecule, altered tertiary structure may result in significantly altered function. Also, the same glucose molecule may form cross-links with two or more amino acids, resulting in altered structure or permeability. Additionally, there is evidence that in the presence of hyperglycemia and non-enzymatic glycosylation of peptide structures, net membrane ionic charge changes over time; there is accumulation of sorbitol and other polyols; there is dysfibrinogenemia and hypercoagulability; and there is impaired endothelial nitric oxide generation. There is also evidence that intracellular free radical formation is accelerated and clearance of free radicals is diminished in the diabetic milieu. All of these, and perhaps other yet-undescribed consequences of the hyperglycemic milieu, contribute to the gradual development of altered capillary basement membrane permeability and small vessel patency which are clinically expressed as recognizable target organ microvascular complications of diabetes.

The natural history of complications in type 2 diabetes differs from that of type 1 diabetes in that dysglycemia often is subclinical for years to decade prior to the actual diagnosis (Figure).
**Diabetic Retinopathy**

Small-vessel disease of the retina occurs in three principle forms:

- **Background retinopathy:** Eventually present in 80-90% of diabetics (about 50% prevalence at 10 years’ duration of diabetes), this form of eye disease is not of itself sight-threatening. It is characterized by the presence of microaneurysms and "dot" hemorrhages and scattered hard exudates.

- **Macular edema ("pre-proliferative retinopathy"):** An intensified form of BDR involving the macula, it is often associated with blurred vision and requires laser treatment for stabilization.

- **Proliferative retinopathy:** Occurs in about 20% of diabetics; defined by the presence of neovascularization usually involving the vessels around the optic disc. Requires laser treatment to avoid the feared complication of retinal hemorrhage leading to detached retina and scarring and/or vitreous hemorrhage.

**Screening:** Dilated funduscopic examination, usually performed by an ophthalmologist or optometrist, is recommended for all diabetic patients on an annual basis. Non-mydriatic digital retinal photographs may also be used to screen and have the advantage of being done in a primary care setting.

**Intervention:** Pan-retinal laser photocoagulation of affected eyes reduces the risk of blindness by at least 50%. Patients who have a vitreous hemorrhage may also benefit from the more invasive procedure of vitrectomy.

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**Diabetic Nephropathy**

Collectively, diabetic renal disease affects about half as many patients as retinopathy. *Over 90% of diabetics who develop renal disease have significant retinopathy;*
therefore, the finding of renal disease in the absence of retinopathy raises concern that the renal disease may be something other than diabetic in origin. In that situation, renal biopsy may be indicated to establish a diagnosis. Usually, however, diabetic renal disease is diagnosed clinically, with consideration of the following typical features:

- **Risk Factors:** Poor glycemic control; hypertension; family history of renal disease

- **Natural History:**
  - **Early Hemodynamic Alteration:** Glomerular filtration rate (GFR) in the "supernormal" range, reflecting glomerular "hyperfiltration" may be present at time of diagnosis of diabetes, and a consistent finding is that GFR decreases towards or into the normal range if normoglycemia can be established.
  
  - **Incipient Nephropathy:** Onset of so-called microalbuminuria: urine albumin excretion rate increases to range of 30-300 mcg/min (normal, < 30), which is still below the rate at which the conventional urine dipstick for protein will register positive. Tends to begin after 5-10 years’ duration of diabetes.

  - **Fixed Proteinuria:** GFR begins to progressively fall, with progression to end-stage renal disease (ESRD) over a period of 3-5 years, sometimes concurrent with the onset of "heavy" (nephrotic-range) proteinuria (> 3 grams/day). In previously normotensive patients, hypertension usually develops at this stage of the disease. Diabetes is the most common identifiable cause of nephrotic range proteinuria in adults. Fixed proteinuria is primarily seen after a minimum of 10 years’ duration of diabetes.

  - **Progressive Azotemia, followed by End-Stage Renal Disease (ESRD):** Once fixed proteinuria appears, azotemia follows soon after. Untreated, renal function in diabetic nephropathy deteriorates at a predictable rate, with about 50% of patients reaching end stage within 5 years. A graph of 1/serum creatinine vs. time is usually charted by nephrologists, who are able to use it to accurately predict when a patient will require dialysis support. Diabetes is the single most common etiology of ESRD in the U.S. The preferred mode of therapy is renal allograft, due to long-term survival benefit that is conferred; in Type I diabetics, concurrent pancreatic transplant to "cure" the diabetes could be considered, to prevent the late recurrence of diabetic nephropathy in the allograft.

**Screening:** Annual measurement of urinary albumin by a method sensitive in the detection of microalbuminuria is indicated in all diabetic patients. Microalbumin is not detected on a routine dipstick urinalysis.

**Interventions:** At the microalbuminuria phase, meticulous glycemic control, antihypertensive treatment, and treatment with an ACE (angiotensin converting enzyme) inhibitor or ARB (angiotensin receptor blocker) can delay the onset of fixed proteinuria. This effect is independent of the effect on blood pressure. *The beneficial effect of ACE inhibitor or ARB drugs are attributable to the selective effect of these agents on the efferent renal arteriole, resulting in reduced glomerular capillary pressure and thus reduced extravasation of protein into Bowman’s space.* In patients with heavy proteinuria and azotemia, effective BP control and ACE inhibitors may also be of benefit, but glycemic control has not been shown to make a difference at that stage. Dietary protein restriction is also helpful, presumably on the basis of limiting the glomerular workload in the excretion of nitrogenous waste. Even in patients with end-stage renal disease who are
on dialysis, glycemic control is important since it has been shown that it improves the 5 year survival rate from 15% to 30%.

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**Diabetic Neuropathy**

There are a couple of common neuropathic syndromes which occur in about 40% of diabetics by 10 years’ duration of diabetes. Both involve stocking > glove distribution; in one form, paraesthesias and burning pain predominate, and in the other, numbness/anesthesia and loss of proprioception and vibratory sensation predominate. Either form may improve with better glycemic control, although not on a consistent basis. Tricyclic antidepressants (like amitriptyline or nortriptyline), anticonvulsants (like gabapentin or carbamazepine), and/or topical capsaicin (derived from hot peppers) cream are often used to palliate painful neuropathy. The greatest morbidity of peripheral neuropathy relates to the development of the insensate foot, which is then susceptible to unrecognized trauma and subsequent infection. It is important to educate the diabetic patient not to walk barefoot; to inspect the feet daily; and to wear professionally-fitted shoes, all with the intent of minimizing injury.

In addition to peripheral sensory neuropathy, many diabetic patients develop syndromes of autonomic neuropathy, which can produce orthostatic hypotension, delayed gastric emptying, constipation and fecal incontinence, overflow neurogenic bladder, impotence (in up to 50% of diabetic men), impaired sweating in response to heat and exercise, gustatory sweats, and hypoglycemic unawareness. These are extremely debilitating problems posing difficult management issues and no easy answers. Silent ischemia is also a result of diabetic autonomic neuropathy because of the impairment of pain pathways of the heart (carried by autonomic neurons) resulting in the frequent observation of abnormal EKG’s due to a silent myocardial infarction.

**Screening and Intervention:** Physical examination of the foot should be done at each scheduled office visit. Particular attention is paid to the condition of the skin, and the presence of calluses, tinea pedis, reddened areas (pre-ulcerations) and any frank ulcerations. Testing with a Semmes-Weinstein 10 gram monofilament should be done yearly to determine if sufficient sensation exists to prevent ulcers. Working closely with a podiatrist and/or orthopedic surgeon (as applicable) is extremely useful. Ulcers are treated aggressively, and it is always vital to rule out osteomyelitis in the patient with a foot ulcer. This usually involves plain x-rays and MRI. *In 2/3 of cases, radiographically confirmed osteomyelitis was not suspected clinically!*

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**Diabetic Atherosclerosis**

Most patients with Type 2 and many Type 1 diabetes eventually die of myocardial infarction (MI), congestive heart failure, or stroke, and many suffer from peripheral arterial disease. Atherosclerotic disease in patients with diabetes contrasts with atherosclerosis in non-diabetics by exhibiting diffuse (as opposed to focal) plaques and more distal (and thus less able to be bypassed) luminal narrowing and irregularity. The small arteries of the lower leg are often calcified in diabetic disease, and rarely so in "garden variety" non-diabetic atherosclerosis. The risk of a major cardiovascular event...
(e.g. MI) in a patient with Diabetes Mellitus who has not previously had an MI is equivalent to the risk of a non-diabetic patient having a second MI. Adding to the risk of large vessel disease in diabetes is a particular form of serum lipid abnormality known as diabetic dyslipidemia. This is characterized by hypertriglyceridemia (predominantly VLDL) and low HDL cholesterol. The LDL cholesterol level is variable but is characterized by a disproportionate amount of small, dense LDL particles which are atherogenic. Treatment of lipid disorders in diabetes usually consists of attempts at optimizing glycemic control (which may lower triglycerides), encouraging dietary saturated fat restriction, and prescribing hypolipidemic drug therapy. Statins (e.g. simvastatin, rosuvastatin, atorvastatin, and pravastatin) are first line drugs. New guidelines for the use of statins were promulgated in 2013 by the American College of Cardiology/American Heart Association that eschew absolute LDL goals (previously the goal was 70 mg/dl). All patients with diabetes (Type 1 or 2) who are ages 40-75 and who are without evidence of cardiovascular disease should be on a moderate dose of a statin. A high dose statin should be used in those patients with diabetes who have a 10-year risk of a cardiovascular event ≥7.5% (a calculator is available on their web site). Graded exercise testing should be considered in all patients with Diabetes Mellitus for more than 15 years to exclude silent ischemia. If normal, the patient should then be given an exercise prescription.

Principles of Glycemic Control

Consider the serum glucose concentration as representing the net sum of opposite processes, glucose production vs. glucose utilization. On the production side, important inputs are, of course, oral food intake, glucose release from hepatic and muscle glycogen stores (glycogenolysis), and glucose formation from substrates such as lactate/pyruvate, alanine, and glycerol (gluconeogenesis). On the utilization side, glucose can be either metabolized anaerobically to lactate/pyruvate or stored as glycogen in the liver and muscle, or used in the production of storage fats (glycerol) and protein. Insulin promotes anabolic glucose utilization: cellular uptake by muscle and fat tissue; glycogen formation; inhibition of lipolysis, hepatic gluconeogenesis, and glycogen breakdown; and inhibition of glycolysis. Insulin is the most dominant hormonal influence in normal glucose metabolism.

Counter regulating hormones have the opposite effect on glucose metabolism: they promote glycolysis, glycogen breakdown, and gluconeogenesis. The counter regulatory hormones, in order of importance, are glucagon, epinephrine, growth hormone, and cortisol. Thus, in states where any one or more of the counter regulatory hormones is elevated (such as stress-induced epinephrine increase, Cushing’s syndrome where cortisol is increased, or acromegaly where growth hormone is elevated), blood glucose tends to be high. In addition, hypoglycemia (blood glucose less than 50 mg/dl) is a major stimulus to the production of all 4 counter regulatory hormones.

Excellent glycemic control is only possible when the patient is educated and motivated to monitor his own blood glucose using a portable glucose meter, act on the results of his testing, and maintain the self-discipline necessary to adhere to a consistent diet and exercise regimen. Diabetes is a demanding disease which can be controlled with appropriate physician advice. However, patient knowledge and compliance is critical to
success. Without this partnership of the physician and patient, diabetes will become a devastating disease!

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**Therapy in Type 1 Diabetes**

Since the discovery of insulin, arguably the most important advance in the care of diabetics has been the use of home blood glucose monitoring. This powerful tool allows the patient and physician to understand and treat the multiple factors affecting glycemic control. All patients with Type 1 diabetes should be monitoring their blood sugars several times a day and present the records to their physician at each visit and/or by fax in the interim. Glucose meters can be uploaded to a desk-top or online programs and their data analyzed statistically and the results displayed graphically.

**Insulin Therapy:** In Type 1 Diabetes Mellitus, the role of insulin is hormone replacement—there is no alternative, and at present, there is no accepted adjunctive medical therapy for the purpose of establishing glycemic control. Insulin therapy in Type 1 patients is predicated according to the principle of simulating two normal effects of insulin: 1) to promote storage of glucose in muscle, fat, and liver tissue when blood glucose normally rises following absorption of carbohydrate from a meal (postprandial effect), and 2) to restrain production of glucose by the liver (from glycogen breakdown [glycolysis] and from protein and fat stores [gluconeogenesis]) during the fasting (postabsorptive) state. It also prevents lipolysis in fat cells so that free fatty acids are not released. The two forms of insulin replacement coverage are often referred to as prandial and basal insulin delivery and the goal is to recapitulate the normal relationship of insulin to glucose (Figure). The importance of liver glycogenolysis and gluconeogenesis cannot be overstated: it is the unrestrained effect of these processes which results in the fasting hyperglycemia noted in most patients with diabetes. One cannot account for an elevated fasting glucose based on a meal 8-12 hours earlier--after such a time lapse, the hyperglycemia would be corrected by the combination of non-insulin dependent glucose utilization by the brain and CNS, and renal excretion of glucose. Hence, the liver represents a major target for insulin effect as we plan for and evaluate the impact of insulin therapy.

**The Price You Pay:** Unfortunately, there remains a fundamental paradox in available insulin delivery systems which attempt to simulate normal physiology. The normal pancreas secretes insulin into the portal circulation, resulting in a substantial first pass effect on the liver. Hepatic gluconeogenesis and glycogenolysis can thus be restrained satisfactorily with a relatively low peripheral blood insulin concentration (except for the postprandial state, when it is transiently high--portal blood insulin levels are even higher.
at this time). By contrast, insulin administered subcutaneously—which is the conventional route of administration—must enter the portal circulation after first reaching the systemic venous circulation. The physiologic consequence is that in order to achieve the desired effect on the liver’s glucose production rate, the price paid is very high (relative to normal) peripheral blood insulin concentration, which results in two clinically undesirable sequelae. On the one hand, high peripheral blood insulin levels in the fasting state may produce hypoglycemia, through inappropriate cellular uptake of glucose by insulin-responsive tissues. Second, accelerated peripheral action of insulin will produce glucose and fatty acid uptake by peripheral tissues resulting in increased adiposity. These "facts of life" are indeed germane clinically, as the two major phenomena observed in otherwise well-controlled diabetics are an increased frequency of iatrogenic hypoglycemia and gradual weight gain.

**Delivery Systems:** Eventual solutions to the paradoxical insulin delivery problems posed by conventional therapy include intraperitoneal implantable insulin pumps, intraperitoneal catheters, and transplanted or synthetic islet cells. For now, the best available practice is the administration of subcutaneous insulin, either via a continuous infusion pump or via multiple daily injections from a syringe. Think of the "pump" as nothing more than an automated syringe, about the size of a beeper, which administers rapid-acting (lispro, aspart, or glulisine) or short-acting (Regular) insulin continuously via a catheter placed subcutaneously. With the pump, one or multiple continuous infusion rates can be programmed by the user. At mealtimes, the user "overrides" the programmed rate and gives a "bolus" dose to simulate the normal pancreatic islet response to feeding. With multiple daily injections, the user provides "basal" insulin coverage with a long-acting (glargine or detemir) or an intermediate (NPH) insulin preparation, and provides mealtime ("prandial") coverage with rapid-acting (lispro, aspart, or glulisine) or short-acting (Regular) insulin shortly before or with each meal. The FDA approved an inhaled insulin in 2014 that has a very rapid absorption (the surface area of the lung is as large as a tennis court). This can be used as a “bolus” but not basal insulin.

**Dosing:** Patients with Type 1 diabetes are notoriously unpredictable in their insulin requirements, so a great deal of individual customization is almost always required in the "fine-tuning"! Nonetheless, you have to begin somewhere, so we usually "guesstimate" a daily insulin requirement of about 0.6 units per kg body weight. For pump patients, we usually split that total daily dose requirement into one-half "basal" (continuous) infusion and one-half "prandial" boluses. **Pump patients usually require about 25% less total insulin per day than those treated by more conventional delivery means.** For multiple daily injection (MDI) patients, a reasonable approach is to give one-third to one-half the total insulin dose as long-acting glargine or detemir at bedtime ("basal dose") and the pre-meal doses of rapid-acting aspart, lispro, glulisine or short-acting Regular before or with meals ("bolus doses"). Patients on pumps or using MDI are also provided with a bolus dosing algorithm, so that they can adjust the mealtime bolus dose according to their current level of glycemia as well as to the carbohydrate content of their upcoming meal. Thus, they would administer a small insulin dose before a meal if the blood sugar is low, and a progressively higher dose for a progressively higher blood sugar; more insulin for a
pasta meal and less for a hamburger. The major elements required for the success of an intensive therapy program are 1) a high level of patient motivation, 2) the willingness of the patient to test the blood glucose regularly, 3) their willingness to adjust the insulin dose according to the blood glucose, 4) their willingness to adhere to a reasonably consistent diet and exercise regimen, and 5) their understanding of the relationship between diet, exercise, blood sugar and insulin dose.

Somogyi and “Dawn” Phenomena

Both the Somogyi and “dawn” phenomena result in morning hyperglycemia but do so through very different mechanisms. The “dawn” phenomenon is the natural rise in blood sugar between 0300 and 0600 resulting from increased hepatic glucose output. The proximate cause of this is the large spikes of growth hormone that occur with Stages III and IV sleep and not the diurnal cortisol rise which occurs at the same time. This normal response is exaggerated in diabetics and may result in a significant rise in blood sugar in this time frame (up to 100 mg\% )! The Somogyi phenomenon is the rise in blood sugar that occurs in response to nocturnal hypoglycemia (which is often asymptomatic). The most common cause of the Somogyi phenomenon is NPH insulin administered pre-supper because its peak actions is 5 to 8 hours after injection – which occurs at a time of greatest insulin sensitivity (0000 to 0300 hours). As a result, it is almost impossible to achieve fasting normoglycemia without risking nocturnal hypoglycemia if one uses pre-supper NPH insulin.

Therapy in Type 2 Diabetes

Because patients with Type 2 diabetes retain some ability to produce endogenous insulin, any insulin therapy in these patients should be regarded as supplemental rather than obligate replacement. It seems that the following statement appears near the beginning of EVERY article ever written about Type 2 diabetes: "The cornerstone of therapy is diet and exercise". Now we’ve gotten that out of the way! Seriously, the statement is correct, and if we could enforce these two elements better, there would be fewer complications with far less pharmaceutical intervention required. For asymptomatic patients with moderate hyperglycemia, we should recommend a trial of treatment involving only calorie-restricted diet (to result in weight loss towards ideal body weight) and exercise (to improve insulin sensitivity, as well as to augment the effect of diet on weight loss). Things being what they are, though, we frequently must resort to pharmacotherapy after a failed trial of diet and exercise. Patients with Type 2 diabetes should monitor their sugars at home – the frequency of which varies according to the therapy and stability of the patient.

The philosophy in treating patients with Type 2 diabetes is to begin with a drug from one class. If this is insufficient in achieving the glycemic goal, a drug from another class is
added rather than increasing the dose of the first drug. There are now 8 FDA-approved classes of drugs (in addition to insulin), each aimed at a different aspect of the pathophysiology: biguanides, insulin secretagogues, thiazolidinediones, alpha-glucosidase inhibitors, GLP-1 analogues, DPP-4 inhibitors, SGLT-2 inhibitors dopamine agonists, bile acid sequestrants. The latter two classes are rarely used.

**Biguanides:**
The only currently available member of this class of oral agent available in the U.S. is metformin (Glucophage) which is generally administered as first line therapy. This agent is well-tolerated by most patients, with occasional exceptions of GI side effects (mostly diarrhea and dyspepsia) and rare instances of lactic acidosis (usually in patients with pre-existing CHF or renal insufficiency (serum creatinine ≥ 1.5 mg% in men and ≥ 1.4 mg% in women)—both are recognized contraindications to therapy). Metformin should be stopped for 24-48 hours prior to any radiographic procedure using iodine-containing contrast material and before any surgical procedure or during any acute medical event (e.g. MI, congestive heart failure) in order to be certain that acute renal failure has not occurred. Advantages of metformin include relative absence of two major undesirable side effects of most other agents: hypoglycemia and weight gain. Its major mechanism of action is restraint of hepatic gluconeogenesis. It can be used in combination with sulfonylureas, with additive efficacy but hypoglycemia may occur due to the sulfonylurea.

**Insulin Secretagogues (Sulfonylureas and others):**
The most popular sulfonylureas in the U.S. are various formulations of glipizide (Glucotrol), glimepiride (Amaryl), and glyburide (DiaBeta, Micronase, Glynase). The primary mode of action of these drugs is to augment the normal "first phase" release of insulin from the islet cell, when stimulated by rising ambient blood glucose following a meal. They also increase insulin receptor number to some degree. These drugs are among the least costly of the oral agents, and for this reason as well as considerable experience, they are the alternate first-line drug. There are some reliable predictors of success when one is debating the use of one of these drugs vs. insulin therapy: likely responders include 1) the obese (who are more likely to have insulin resistance, as opposed to insulin deficiency, as the primary defect); 2) those with relatively mild hyperglycemia (fasting glucose < 250 mg/dl); and 3) those who do not manifest ketosis in the postprandial state (presence of ketosis reflects insulin deficiency, and a need for supplemental treatment). A past history of ketoacidosis should preclude the use of these agents, based on the known mode of action.

Repaglinide (Prandin) and nateglinide (Starlix) are non-sulfonylureas that rapidly stimulate insulin release and have very short half-lives. They come closest to mimicking short-acting insulin injection and may be advantageous in patients who need only a “whiff” of treatment or in those with mild renal insufficiency (renal insufficiency prolongs insulin clearance and thus enhances the effect of any insulin or insulin secretagogue).

**Thiazolidinediones (Actos – pioglitazone; Avandia - rosiglitazone):** Thiazolidinediones have as their mechanism of action the enhancement of peripheral tissue insulin sensitivity. They are used effectively in insulin-resistant patients on other oral agents or
in those patients requiring large insulin doses with the resultant reduction in insulin dose. Liver function tests should be monitored regularly in patients treated with all thiazolidinediones, because the major recognized untoward effect is serious chemical idiosyncratic hepatitis (hepatonecrosis). Weight gain is common with these drugs and peripheral edema (whose etiology is currently unknown) is also a common side effect precluding their use in patients with significant cardiovascular disease or a history of congestive heart failure.

**Alpha-glucosidase Inhibitors (Precose - acarbose and Glyset - miglitol):** These agents have a unique mode of action: they cause delayed absorption of carbohydrates from the gut, thus preventing native "first phase" insulin secretion from being overwhelmed by a postprandial glycemic surge. They can be used in combination with any oral agent, and with insulin. Known side effects are entirely of a GI nature: mostly bloating/nausea in overeaters and flatulence in most patients (sort of an "Antabuse" for overeaters, maybe?). Efficacy tends to be mild to moderate at best and the GI side effects generally preclude their use.

**GLP-1 Analogues:**
The first of these agents, exenatide (Byetta ®), was approved in June 2005 and a second, li raglutide (Victoza) was approved in early 2010. GLP-1 is an incretin hormone secreted by the L-cells which is deficient in patients with Type 2 diabetes. It has a myriad of physiologic effects. It stimulates insulin release from the beta cell (explaining the higher insulin levels after oral intake vs. intravenous infusion of sugar), suppresses glucagon from the alpha cell thereby reduces hepatic gluconeogenesis and glycogenolysis, delays gastric emptying thereby reducing the speed with which food reaches the small intestine, and reduces appetite with resultant weight loss. It must be given by SQ injection twice daily (exenatide) or once daily (li raglutide). A long-acting SQ preparation of exenatide (Bydureon) is available. It is injected once a week.

**DPP-4 Inhibitors:**
Dipeptidyl peptidase is a ubiquitous enzyme with up to 12 isomers which cleave many peptides include GLP-1. The DPP-4 inhibitors, sitagliptin (Januvia®),saxagliptin (Onglyza®), and linagliptin (Tradjenta®) inhibit the DPP-4 action. By doing so, the levels of endogenous GLP-1 are raised and the intrinsic action of this hormone is enhanced.

**SGLT-2 Inhibitors:**
Sodium-glucose co-transporter 2 (SGLT2) inhibitors act on renal SGLT2 and block the reabsorption of glucose in the proximal tubule. This increases glucose excretion and lowers blood glucose levels. Two drugs have been approved in this class so far – canagliflozin (Invokana) and empagliflozin (Jardiance).

**Insulin:**
Supplemental insulin dosing in Type 2 patients usually begins with the addition of a bedtime long-acting insulin such as glargine or detemir. Alternatively, NPH can be given at bedtime but the frequency of nocturnal hypoglycemia is higher than with glargine or detemir. Dosing initially starts with 0.1-0.2 units/kg body weight. The theory is that the
insulin will work primarily to restrain hepatic gluconeogenesis during the overnight fast resulting in less weight gain over the long term. However, in general, the risk of nocturnal hypoglycemia is small with this regimen because of the “dawn” phenomenon. Insulin can be given in similar regimens as in Type 1 patients but this generally is associated with discontinuation of the oral agents.

**Hypoglycemia in Diabetics**

The most common day-to-day complication of sulfonylureas, metiglinides and insulin is “iatrogenic”hypoglycemia. Worldwide, sulfonylureas cause the most hypoglycemia, since Type 2 diabetes is the more common form and these drugs represent the most popular therapy. Adrenergic symptoms of hypoglycemia arise when epinephrine production is stimulated by a falling serum glucose. These include nervousness, tremor, increased sweating, and rapid palpitations. Neuroglycopenic symptoms develop when the CNS is no longer able to transport glucose rapidly enough to sustain normal function; these symptoms include blurred vision, diplopia, confusional states, amnesia, seizures, and loss of consciousness/coma. In patients with longstanding Type 1 diabetes, adrenergic symptoms tend to disappear over time, leaving the patient vulnerable to sudden attacks of compromised cerebral function. This phenomenon is known in the literature as hypoglycemia unawareness. Such patients require recognition by health providers, because glycemic control goals may have to be relaxed somewhat to permit normal daily function. At times, it may be necessary to counsel patients with frequent severe hypoglycemia not to operate a motor vehicle, since cerebral dysfunction can (and often has) resulted in traffic accidents.

Treatment and prevention of hypoglycemia emphasizes patient education and self-monitoring. It is prudent for susceptible patients to test blood glucose prior to exercise or periods of driving. They should carry quickly-absorbed carbohydrates for an emergency food source; glucose gel is a good product, and glucose tablets, Life Savers, and small cans of sweetened fruit juice are all acceptable. Urgent treatment of hypoglycemia includes subcutaneous, intramuscular or intravenous injection of glucagon (1 mg) or infusion of one ampule of 50% dextrose solution intravenously. Continuous 10% dextrose should be administered intravenously following urgent resuscitation.

**Hypoglycemia in Non-Diabetics**

Patients with blood glucose values of less than 50 mg/dl associated with symptoms (see below) have clinically relevant hypoglycemia. Whipple’s triad is used to officially define this syndrome – blood sugar under 50 mg/dl, symptoms consistent with hypoglycemia, and resolution of these symptoms with correction of the low blood sugar.

There are 2 types of symptoms related to hypoglycemia – adrenergic and neuroglycopenic. The former are mediated by catecholamines and include diaphoresis, palpitations, anxiety, and headaches, while the latter is characterized by confusion, irritability, abnormal behavior, seizures, and ultimately coma.
Hypoglycemia present in the fasting state usually results from organic causes while post-prandial hypoglycemia (so-called reactive hypoglycemia) may be related to alimentary causes (previous GI surgery, peptic ulcer disease, or GI dysmotility syndrome) or may be idiopathic - a “functional” (read psychologic) disturbance. As a rule, fasting hypoglycemia presents with neuroglycopenic symptoms and post-prandial hypoglycemia usually has only adrenergic symptoms. However, while important for classification, patients may have both types of symptoms in each category.

Fasting hypoglycemia is usually caused by one of the following: pancreatic diseases (insulinoma or nesidioblastosis); hepatic disorders (cirrhosis of any etiology, congenital disorders of glycogen storage); pituitary-adrenal disorders (hypopituitarism, Addison’s disease); non-pancreatic tumors (large mesodermal tumors such as leiomyosarcoma or fibrosarcoma); exogenous causes (iatrogenic related to treatment of diabetes with either insulin secretagogues or insulin itself, or factitious which is usually seen in paramedical personnel). Hypoglycemia can also be artifactual (pseudohypoglycemia) which is seen which white blood cell counts are markedly elevated such as in leukemia. This is not associated with symptoms and thus does not fulfill Whipple’s triad. Finally, alcohol can cause hypoglycemia by acutely inhibiting hepatic gluconeogenesis through alterations of the cytosol NADH2/NAD ratio and by inhibiting epinephrine and growth hormone counter-regulatory secretion to the hypoglycemic stress. This occurs with even relatively small amounts of alcohol (100 g) in patients with patients who already have impaired ability for gluconeogenesis or glycogenolysis (e.g. fasting or malnutrition, infiltrative liver diseases).

The mechanism of hypoglycemia due to non-islet cell neoplasms may be multifactorial. Tumor-related malnutrition causes reduction in hepatic gluconeogenesis and glycogen stores are diminished. Rarely, some tumors utilize a large amount of glucose and/or secrete insulin-like growth factors (e.g. IGF-1 or IGF-2).

The laboratory tests which are the most useful in the evaluation of fasting hypoglycemia are simultaneous insulin and glucose levels. If there is an elevated insulin/glucose ratio, a C-peptide and/or a sulfonylurea level may be useful to rule out factitious hypoglycemia. C-peptide is the amino acid section cleaved off of pro-insulin to create insulin, and its absence at the time there is an elevated insulin level suggests that there is exogenous administration of insulin as the cause of the hypoglycemia. The presence of insulin antibodies also suggests the exogenous administration of insulin. If the insulin/glucose ratio is low, a non-insulin-mediated cause should be sought. Renal and liver function testing should always be done.

If a patient is suspected of having an insulinoma, they may need to have a supervised 48-72 hour fast with glucose and insulin measurements every 6 hours. Most cases are diagnosable within the first 24 hours. Patients with insulinoma should be screened for other endocrine neoplasias as they may have the familial multiple endocrine neoplasia (MEN) type I syndrome. Family members should also be screened.
The Diabetic Office Visit

Obviously, each diabetic patient is an individual, and will predictably have unique care needs, including non-diabetic-related health issues and conditions. Notwithstanding, the following guidelines constitute a reasonable summary of best current practice, and should help you to organize your approach to a diabetic patient during clerkship experiences. Such an approach allows us to review the patient’s diabetes-specific knowledge, motivation, self-care habits, and whether or not any complications of the disease are present:
<table>
<thead>
<tr>
<th>Area of Concern</th>
<th>To Do:</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic Control</strong></td>
<td>Interval History:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Review fingerstick glucose diary</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Frequency &amp; severity of hypoglycemia</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Diet/Exercise regimen compliance</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Nocturia, fatigue and other symptoms</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin A1C</td>
<td>Quarterly</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol/HDL/LDL/Triglycerides</td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Eye Disease</strong></td>
<td>Interval History:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Change in visual acuity?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>Comprehensive Ophthalmology Exam</td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Renal Disease</strong></td>
<td>Interval History:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Edema?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Known change in BP?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>BP measurement</td>
<td>Annually</td>
</tr>
<tr>
<td></td>
<td>Urine test for &quot;microalbumin&quot;</td>
<td>biannually (if renal insufficiency present)</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance</td>
<td></td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>Interval History:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Foot ulcers?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Numbness or tingling in feet?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Nocturnal foot pain (burning)?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Impotence?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>Physical Exam of the feet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pulses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Condition of skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Deformities of toes/nails?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Light touch/vibratory sensation or nylon monofilament test, ankle jerks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review Preventive Care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Patient to inspect feet daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Report any injury promptly!</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DON’T GO BAREFOOT!!</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DON’T SMOKE!!</td>
<td></td>
</tr>
<tr>
<td><strong>Atherosclerotic Disease</strong></td>
<td>Interval History:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chest Pain?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Dyspnea/othe CHF symptoms?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Numbness/weakness of one arm/one leg/one side of face?</td>
<td>Each Visit</td>
</tr>
<tr>
<td></td>
<td>• Claudication?</td>
<td></td>
</tr>
</tbody>
</table>
Physical Exam:
- Cardiac auscultation
- Femoral pulses
- Carotid/femoral/aortic bruit?

EKG

Serum Lipid Screening

<table>
<thead>
<tr>
<th>Related Health Conditions</th>
<th>Serum TSH</th>
<th>Annually (in Type 1’s)</th>
</tr>
</thead>
</table>

Returning to your first patient....

What other questions do you need to ask her?

This patient has had relatively recent onset of her symptoms. You should question her as to the pattern and frequency of her urinary symptoms, what types of fluids she is drinking for her symptoms of thirst, and if she has gained or lost weight with her polyphagia. You also would want to know if she has had a recent treatment with corticosteroids or experience a recent medical stress such as a febrile illness. Also, you should ask questions that might elicit symptoms or signs of Cushing’s syndrome or acromegaly. You need to take a careful family history to ascertain whether or not there is an autoimmune diathesis in first degree relatives, a history of Type 2 DM, or premature cardiovascular events. The social history is particularly important with respect to alcohol use.

What else should you look for on physical exam?

Examination of the fundi might lead to some clues as well as a careful cardiac and neurologic examination. Evidence of secondary causes of hyperglycemia such as Cushing’s syndrome or acromegaly.

Do you need to order other tests?

Visual examination of the blood might be helpful but serum lipid levels should be definitive. An A1C and fructosamine level will give clues to the duration of the hyperglycemia. Antibodies to GAD, islet cells, IA-2, and/or insulin would help determine whether or not the patient has autoimmune diabetes. Other studies of hepatic function and the etiology of transaminasemia should be done to exclude infectious and infiltrative processes.

What treatment is the most appropriate for her?

Hydration and insulin should be initiated. The patient has new onset Type 2 diabetes with mild ketoacidosis. The xanthomas represent severe hyperlipidemia that often accompanies deterioration in glycemic control. Hypertriglyceridemia and hyperglycemia have, in and of themselves, deleterious effects on beta-cell function - so-call lipotoxicity and glucotoxicity – creating a vicious cycle. Once her hyperglycemia is treated with insulin, she may be able to be transitioned to oral agents. Her hyperlipidemia may also improve so that initiation of pharmacotherapy should await normalization of her blood sugar.
Your next patient…
While stationed in Afghanistan, a 39-year-old Army National Guard soldier presents to his troop medical clinic with a two month history of increased urinary frequency, having to get up several times during the night to urinate and having his need to urinate interfere with his patrol duties. He also has had blurred vision over the past month, initially attributing it to the wind picking up sand or dust, but acknowledging that it seems to be a problem even when he has not been outside.

What other questions should you ask?
First, especially in this setting, you want to ask about head injury, since traumatic brain injury (TBI) could damage the pituitary or hypothalamus, causing a central diabetes insipidus. He fortunately does not have any history of TBI. Second, you want to ask about polydipsia and polyphagia, the other two of the “3 P’s” characteristically associated with diabetes mellitus; he does in fact acknowledge that he has been drinking lots of water and Gatorade, but thought he should be keeping well hydrated in the hot environment. He has been snacking in addition to eating 3 meals ready to eat (MREs) per day. You also want to ask about dysuria, hematuria, flank pain, and fever, which could indicate prostatitis or a urinary tract infection. He denies any of these symptoms.

What should you check on physical exam?
You should check vital signs as well as height and weight, and you should calculate a body mass index (BMI). You should do an eye exam, including an assessment of visual acuity and a funduscopic exam. You should do a neurologic exam, a digital rectal exam to check the prostate for bogginess and tenderness, and a check for flank tenderness to percussion. Except for a BMI of 29 and 20/50 vision bilaterally, his physical exam is unremarkable.

What laboratory testing should you obtain?
You should order a complete blood count to check his white blood cell count, as well as serum chemistries to assess his sodium, potassium, kidney function, and glucose. You should also check a urinalysis and urine culture. His blood glucose is 240, while other test results are unremarkable.

What causes of his polyuria and blurred vision should you consider?
Your history suggests that diabetes mellitus is most likely. Laboratory testing confirms this diagnosis, while your physical exam and other lab tests rule out DI, UTI, and prostatitis.

Should he be evacuated from Afghanistan?
It will likely be difficult to provide a new diabetic with the counseling, initial treatment, and monitoring that he needs while in Afghanistan, so evacuation from theater will likely be necessary. However, a motivated soldier with a relatively mild case might be able to remain if in an occupational specialty and duty station where symptoms are unlikely to interfere with duties, diet can be controlled, exercise is possible, monitoring is available,
and you believe that there is a high likelihood of success with diet and exercise alone. Unless a prompt response to diet and exercise is anticipated, a medical board and medical profile are also likely to be necessary.
ICR Polyuria Cases
The small group cases for this session will be the 3 patients that you will discuss as part of your Integrated Clinical Skills (ICS) experience on this topic.

Please complete the form on the next page for the patient that you wrote up during your ICS session.
Please be prepared to give a 3 to 5 minute presentation of this patient for your ICR session. Your ICR preceptor will ask for someone to present each of the three cases.
Name: 
Session topic: 
Patient 
number: 

Summary statement (1-3 sentences)

Prioritized problem list
1.
2.
3.
4.
5.
6.

Prioritized differential diagnosis (include at least 3 diagnostic options)
1.
2.
3.
4.
5.

Justification for leading diagnosis (history and physical exam findings and any ancillary data provided; write as a paragraph):

Plan (diagnostic work-up and/or therapeutic)
1.
2.
3.
4.
Introduction to Clinical Reasoning
GROWTH DISORDERS

Andrew J Bauer, MD
Matthew D Eberly, MD

Practice Case 1:
A 9 year-old boy comes to clinic for a camp physical exam and his father notes that he has not grown very much this past year. You confirm this upon review of his record. On his growth curve at 7 years of age he was at the 25\textsuperscript{th} percentile for height, at age 8 he was just above the 10\textsuperscript{th} percentile and now he is below the 10\textsuperscript{th} percentile for height. Yet, he has been gaining weight appropriately and is at the 10\textsuperscript{th} percentile for age. Should you be concerned?

Practice Case 2:
A 3 year-old male presents to your clinic as a follow-up appointment from the pediatric ward. You find that the child was admitted for 5 days for an “asthma flare.” You discover that the child has been hospitalized four times in his life beginning at age 9 months for “wheezing” episodes. You plot today’s height and weight on the growth chart of the electronic medical record and notice that he is 25\textsuperscript{th} percentile for height, but now <5\textsuperscript{th} percentile for weight. You wonder if anyone else has noticed that he has fallen off the growth curve. Could this patient have an underlying treatable condition?

Objectives: By the end of this session, the student should:
1. Understand that growth and development follow predictable patterns
2. List common causes for growth failure by age: prenatal, birth to 2 years, pubertal
3. Recognize key history and physical examination findings to help establish the cause of growth failure

Readings: Current Diagnosis & Treatment: Pediatrics, 20\textsuperscript{th} edition; access online via LRC. Assigned sections in Chapter 32: General concepts, Hormone types, Feedback control of hormone selection, Disturbances of growth, Target height and skeletal maturation, Short stature, Thyroid physiology, Hypothyroidism, Abnormalities in female pubertal development and ovarian function, Abnormalities in male pubertal development and testicular function, and Adrenocortical hyperfunction

Overview: Since problems in almost any system or organ may cause growth failure in a child, it is important to have an organized approach to the child who presents with short stature and/or a decreased growth rate. There are many different ways to organize such an approach. This section will demonstrate how key findings, heuristics, and basic disease patterns (pattern recognition or basic illness scripts), can be used in the diagnostic approach to growth disorders.

NORMAL GROWTH
In order to recognize abnormal growth, it is important to first know the normal growth pattern. Normal growth is the result of the proper interaction of genetic, nutritional, metabolic, environmental/social, and endocrine factors. It is imperative that growth is monitored especially during well-child exams because growth is a sensitive indicator of health. Poor growth and poor weight gain of any etiology places the young infant at risk for impaired maturation of the neurons in the brain and developmental delay.

One way to understand growth is to discuss the stages of growth and development. The stages of growth can be broken down into intrauterine life, infancy, childhood, and adolescent.

**Childhood Average Growth (cm per year)**

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>First year</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Second year</td>
<td>11.5</td>
<td>12</td>
</tr>
<tr>
<td>Third year</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Fourth year</td>
<td>8</td>
<td>7.5</td>
</tr>
<tr>
<td>Age 5 until puberty</td>
<td>5-6</td>
<td>5-6</td>
</tr>
<tr>
<td>Puberty</td>
<td>28</td>
<td>20</td>
</tr>
</tbody>
</table>

The fastest growth rate of an individual over his or her lifetime occurs during the intrauterine period. Typically, growth velocity during this time averages a rate of nearly 68 cm/year. Maternal factors are the greatest determinant of birth size in this time period.

In the first year of life, the average growth rate is 20 cm/year. It is also in the first 1-2 years that infants start to grow according to their genetic potential. They may start to “channel” or cross percentiles. After the first 2 years of life, crossing percentiles is not considered to be normal.

After the first year of life, the rate of growth starts to decrease. Childhood growth rate ranges from 5-7 cm/year. A child experiences growth failure if the growth rate is less than 5 cm/year. Height and weight may cross percentiles in first 1-2 years of life as genetic factors outplay intrauterine factors. Decreasing, or crossing percentiles after 18-24 months is abnormal. Of note, the slowest growth occurs just prior to puberty.

During puberty, the growth pattern is distinct. During this phase, one has to know the pubertal stage in order to assess whether growth is normal or abnormal. Typically, the start of puberty is often manifested with breast development in females and an increase in testicular volume in males. Testicular volume (TV) is measured using an instrument called an orchidometer, which contains a series of wooden or plastic beads on a string. A testicular volume >3 ml is considered to be pubertal and TV <4 ml is considered to be prepubertal.

Peak height velocity (PHV) occurs 18-24 months earlier in girls than in boys. Peak weight
velocity in girls occurs 6-9 months after PHV. However, in boys peak weight velocity occurs with PHV. The mean growth after menarche is 7.5 cm on average. Fusion of growth plates in boys occurs on average 2 years later than in girls. This allows for a greater interval of pubertal growth, resulting in greater height achieved during pubertal growth spurt. The average pubertal height gain in girls is 20 cm, while in boys it is 28 cm. By the time a patient attains Tanner V sexual maturation, 98% of growth has been achieved.

Growth is also dependent on sex hormones (testosterone and estrogen). Estrogen is the hormone responsible for fusion of growth plates in both men and women. Estrogen potentiates GH secretion (age dependent) and IGF-1 axis. This is why there is a growth spurt, i.e. an increase in growth velocity in puberty. Growth hormone and thyroid hormone are also important for linear growth during this time, but to a lesser extent than in childhood.

GROWTH DISORDERS: AN INTRODUCTION
Since problems in almost any system or organ may cause growth failure in a child, it is important to have an organized approach to the child who presents with short stature and/or a decreased growth rate. There are many different ways to organize such an approach. Perhaps begin by asking when the child's growth was first abnormal. Since different factors are important for growth at different times in a child's life, this allows a quick narrowing of the differential diagnostic possibilities.

Prenatal growth failure
The most important factors for normal growth prenatally are insulin, nutrition (and placental function), and the general genetic endowment of the child. Thus the child with excess prenatal insulin (usually because of maternal hyperglycemia) is born large for gestational age (LGA) and because insulin is an anti-maturational factor, may have immature lungs for his gestational age and exaggerated hyperbilirubinemia.

Adequate nutrition to the fetus may be influenced by the health of the placenta, by maternal hypertension and/or vascular disease, by maternal malnutrition (particularly if it is severe, or if the mother has not yet attained her mature size), and by congenital infection.

Further, the newborn with chromosomal anomalies is usually born small and will continue to be smaller than normal throughout his or her life.

NOTE: Thyroxine and growth hormone, two hormones which are very important to growth later in life, do not have significant effects on prenatal growth. Thus both the baby with congenital hypothyroidism and the one with growth hormone deficiency are typically born with a normal length and weight.

Growth failure beginning between the ages of birth and 2 years
Thyroid hormone is important for bone health and brain development. Because untreated congenital hypothyroidism is an irreversible cause of mental retardation, all states require that all newborns are screened for this. One important role for any physician caring for babies is to ensure that the screen was performed and the result noted in the chart. Treating early (within the first weeks of life) results in an excellent long-term prognosis for both normal growth and mental
Despite the requirement for newborn screening, some children will present with growth failure as a result of inadequate thyroid hormone. This may occur at any time after birth and thus all children failing to grow normally warrant thyroid studies.

Growth hormone deficiency typically presents with some slowing of growth during the first two years, but growth rate then becomes frankly abnormal after the age of two and children with growth hormone deficiency then deviate further and further from their normal growth curve. Nutrition must be adequate throughout childhood and adolescence for normal growth. Chronic disease (infection or inflammation) may also present with growth failure.

**Growth failure beginning between the ages of 2 and puberty**

Insufficient growth hormone, thyroid hormone, or nutrition may each result in a decrease in growth rate. Typically the child with poor nutrition will exhibit decreased weight gain before his or her height falls off the curve. However, this is not always the case, and it may be difficult to sort out the role of nutrition in some cases.

The child with GH deficiency or hypothyroidism is typically slightly "chubby" and will appear immature for his or her chronological age. With true deficiency of either of these hormones the growth rate should be frankly abnormal. That is, they will not only be short, but will also be growing at a less than normal growth rate (5 cm per year is usually felt to be the lower limit for a normal growth rate during this part of childhood.)

**Pubertal growth failure**

The same factors continue to be important for growth during the pubertal years. However, during puberty there is a significant increase in the rate of growth, resulting from the action of sex hormones on bone and by the increase in GH secretion seen with puberty. This occurs earlier in girls than in boys. Boys with a familial growth pattern of delayed puberty and therefore a delayed pubertal growth spurt will often present unhappy at ages 12-15 years because of the widening disparity between their growth rate and that of their peers. Of note, gonadal failure does not cause short stature, but rather failure of signs of maturation and lack of pubertal growth spurt. Growth typically continues at the pre-pubertal rate.

Note "acquired" true growth hormone deficiency may result from a CNS tumor (usually a craniopharyngioma) and therefore all children who appear to have growth hormone deficiency beginning after the third year of life should have an imaging study performed (e.g. MRI) to rule out such a lesion.

For every child with true growth hormone deficiency there are undoubtedly one hundred with growth failure because of nutritional defects (either caloric or specific), drug effects (methylphenidate or glucocorticoids), or genetic short stature with or without a pattern of constitutional delay of growth and development.
HOW TO EVALUATE GROWTH ABNORMALITIES
Using a systemic approach, important historical factors need to be ascertained in order to assess growth abnormalities appropriately:

Prenatal (maternal) History
- History of poor weight gain in mother
- Hypertension; preeclampsia; diabetes
- Singleton or multiple gestation
- Medications, smoking, alcohol
- Infectious diseases: exposure to viruses (CMV, rubella); exposure to raw meat, cats (toxoplasmosis)

Birth History
- Gestational age at birth
- Anthropometrics = length, weight, and head circumference
- Metabolic: hypoglycemia, hyperbilirubinemia, hepatitis, rickets of prematurity, hypotension, hypoxia/anoxia, intraventricular hemorrhage (IVH), rickets of prematurity, necrotizing enterocolitis (NEC)

Infancy, childhood, and adolescence
- Diet
- Social environment and stressors
- Recurrent or chronic medical conditions: ER visits, hospitalizations, surgeries

Medications
- Steroids - multi-factorial effects on growth. All forms of steroids, to include topical for dermatitis/eczema, nasal steroids for allergic rhinitis, inhaled or oral steroids for asthma, may negatively affect growth.
- Amphetamines - medications used to treat attention deficit/hyperactivity disorder (ADHD) decrease appetite and ultimately affect growth.
- Oncology medication and treatment: hypothalamus and pituitary are radiosensitive and may be damaged resulting in growth hormone and/or thyroid hormone (TSH) deficiency.

Development
- Assess if at age appropriate milestones (use Denver Development scoring system).

Diet
- Excessive juice intake in the first year of life (in childhood excessive juice and/or soda intake is associated with increased incidence of obesity)
- Inadequate diet and caloric intake: will lead to energy imbalance and may ultimately have negative impact on linear growth.

Family History
- Parents and siblings height and age when puberty occurred
- Constitutional Delay in Puberty - if one parent has a history of entering puberty late, then child will have 40% likelihood of same (two parents = 60%).
**Review of Systems**
- Head to toe approach
- Sleep habits and energy level: keeps up with peers?
- Headaches and/or visual complaints: CNS lesion?
- Abdominal/GI complaints: growth failure may be first sign of inflammatory bowel disease

After obtaining a thorough history and review of systems, the growth must be plotted on a growth curve. It must include weight, height, and head circumference. *One point in time is not enough to be able to assess growth.* After the age of 2, standing heights are obtained and plotted on appropriate curve for 2-18 year olds. The 0-36 month curves are for supine lengths. Also keep in mind that there are multiple other curves available for premature infants and various syndromes (Turner and Down syndrome being the most common).

Where is the person on the growth curve? This can be defined in 3 ways. The usual way is the height percentile based on the chronologic age defined by birth date. The second method is by using height age which take patient's current height and drawing a horizontal line until it intersects the 50th percentile line. Finally, a bone age is a standardized assessment of growth plate maturation of the left hand. One compares the patient's bone age to standards (Gruelich and Pyle) to assess if it’s delayed, concordant, or advanced. Standards are organized by sex and age of growth plate maturation. Bone age provides valuable information only in the context of the history and physical exam.

In reviewing the growth curve, one has to ask how the patient came to the current height and weight. For example, did they cross percentile lines? If so, at what age? What is their current linear growth velocity (assess with two points at least 6 months apart)? Is both height and weight affected? If so, which parameter (weight or height) decreased first?

Malnutrition has a predictable growth pattern with weight affected (falling away from the curve) before height. Head circumference which is a reflection of brain growth is the last parameter to be affected. It is preserved until extreme malnutrition.

Usually, if height is more affected than weight then an endocrine cause is higher on the differential diagnosis (i.e. Growth hormone or thyroid hormone deficiency). In Cushing's syndrome, there is linear growth failure in the face of increased weight (glucocorticoid excess).

Also, plot the mid-parental height prediction which provides the percentile range a child should be growing at based on height of parents.

**Physical Exam**
- General appearance, developmental milestones, and interaction with environment and parents
- Vitals: heart rate, respiratory rate, blood pressure, and pulse oximetry
- Physical findings with particular significance in evaluation of Growth failure
  - Dysmorphic features
  - Mid-line abnormalities: cleft lip/palate, abnormal tooth eruption (single central incisor), wandering nystagmus, unilateral strabismus, papilledema
- Skin: hypo/hyperpigmented birthmarks (neurofibromatosis, tuberous sclerosis)
- Cardiac: murmur
- Respiratory: clubbing, wheezing
- Abdominal: bloated appearance (with proximal extremity muscle wasting is classic for Celiac's disease), mass
- Genital exam
  - Pubertal staging (Tanner)
  - Ambiguous genitalia
  - Micropenis (growth hormone deficiency)
- Proportions
  Upper:Lower segment ratios
  (lower segment = measure from symphysis pubis to the ground)
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Birth</td>
<td>1.7 : 1</td>
</tr>
<tr>
<td>3 years</td>
<td>1.3 : 1</td>
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<tr>
<td>7 years</td>
<td>1 : 1</td>
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**Differential Diagnosis**

**Genetic Short Stature**
Genetic short stature is defined in adult males as height less than 66 inches and in females less than 61 inches. In the history, one or both parents are short and there is a negative past medical history, negative Review of Systems, and normal physical exam. In these individuals, height may cross percentiles within the first 18 months, then resumes normal growth rate as defined earlier. If a bone age is obtained it would be consistent with the chronologic age. These individuals have no delay in puberty.

**Constitutional Delay of Growth and Puberty**
These individuals are otherwise healthy. They have short stature but have normal growth velocity. There is a positive family history, i.e. parent or sibling with GDGP with 40-60% incidence. In constitutional delay, these children acquire and lose teeth at a delayed age, have a delayed bone maturation (bone age), and experience puberty and the pubertal growth spurt later than usual. Since they grow for a longer time before they fuse their epiphyses and stop growing, they usually end up taller than predicted from their childhood growth percentiles.

Constitutional delay can be assessed by obtaining parental history of pubertal milestones. Typically menarche after 13 years-old is considered delayed as well as a father who continues to grow after high school. Height may cross percentiles within first 18 months then continues to have normal growth velocity. Bone age is consistent with height age which is younger than the chronologic age. The final height based on the bone age is appropriate for mean parental height. With this entity, patients may experience psychosocial stress due to their younger appearance and short stature in comparison to their peers, with boys being affected more than girls.

**Intrauterine Growth Retardation**
Infants with low birth length and weight for gestational age may never have catch up growth the first 1-2 years of life and thus their final adult height is compromised.
**Chronic Malnutrition**

Most common cause worldwide of growth failure is chronic malnutrition. Any gastrointestinal (GI) disease such as Crohn's disease, ulcerative colitis, or celiac disease may present with growth failure. Though these illnesses usually present with GI related symptoms, the very first sign may be growth failure.

Other entities such as anorexia nervosa or bulimia may be associated with growth failure and/or failure to enter or complete puberty. Excessive exercise (gymnasts, figure skaters, ballerinas) also have similar clinical presentation.

**Syndromes**

Many syndromes are associated with growth failure. Many are rare conditions, but together they represent a fairly common etiology for growth failure. One example is Turner's Syndrome (45 XO). With the XO phenotype, 100% of these individuals have short stature with variation in the other associated stigmata. Turner’s syndrome is associated with webbing of the neck (pterygium colli), cubitus valgus, low hairline, shortened 4th metacarpal, hyperconvex nails, or multiple nevi. Cardiac manifestations include bicuspid aortic valve and aortic stenosis. The can have renal anomalies, hypothyroidism, and skeletal abnormalities.

Prader-Willi is associated with growth failure and hypotonia in infancy, followed by uncontrolled, excessive eating and weight gain.

Other examples include Down syndrome, Russell-Silver syndrome, Noonan syndrome, Cornelia de Lange, and Seckels syndrome.

**Endocrine Causes of Growth Failure**

Hypothyroidism can present with deceleration of linear growth. Other physical features associated with hypothyroidism are puffy face, or sallow/sullen expression. All newborns are screened for congenital hypothyroidism but one cannot rely on results in the face of growth failure. If there is concern for growth failure, repeating thyroid function labs is crucial.

As mentioned, congenital hypothyroidism is screened for in all states (via total T4), BUT this may miss infants with pituitary disease, infants with ectopic thyroids (may have sufficient thyroid hormone production initially then be unable to sustain), and auto-immune disease that develops later. In infancy it is very important to identify and treat early to prevent permanent detrimental effects on the brain.

Another endocrine cause of growth failure is growth hormone deficiency. Isolated GHD is uncommon (1/15,000). Severe or complete growth hormone deficiency will present in newborn period with hypoglycemia and micropenis in the male.

Glucocorticoid excess is yet another rare cause of endocrine related growth failure. These patients may have growth failure without cushingoid appearance (in the setting of increased weight) or other physical findings such as round facies, intrascapular fat pad (buffalo hump),
increased body hair, striae, and bruising. These patients also tend to be hypertensive.

If disproportionate short stature is found, one has to consider achondroplasia and hypochondroplasia. These disorders will not be discussed in detail here.

**Other Chronic Diseases of Childhood associated with potential Growth Failure**

**Pulmonary disease**
- Asthma: disease and/or treatment
- Cystic Fibrosis

**Hematologic**: sickle cell anemia, Thalassemia major, Fanconi anemia

**Cardiac**: hypoxic and non-hypoxic congenital heart disease

**Renal disease**: renal tubular acidosis, chronic renal failure

**Psychosocial Dwarfism**
- Growth hormone deficient state secondary to neglectful and/or abusive environment -
  - Physical exam and biochemical testing identical to growth hormone deficiency
- Once patient is placed in an enriching environment, they will thrive and experience catch-up growth

**Laboratory and Radiologic Evaluation**

The Insulin-like growth factor 1 (IGF1) is a surrogate marker for evaluation for GH deficiency. However, it can be negatively affected by poor nutrition. There is also considerable overlap with normal values. It is important to evaluate an IGF-1 level in context of bone age, not chronologic age.

Growth hormone stimulation testing can also be performed to evaluate for GH deficiency as a cause of growth failure. The standard is to administer 2 separate growth hormone secretagogues (Insulin, glucagons, L-dopa, arginine, or clonidine) and measure GH level at 0, 30, 60, 90, and 120 minutes. Values <8-10 ng/ml are consistent with GH deficiency.

**Screening Labs/Radiologic studies**
- CBC with differential
- ESR (erythrocyte sedimentation rate)
- Serum electrolytes and liver function tests (LFTs)
- Urinalysis
- Thyroid Functions: TSH and free T4 (must be euthyroid to perform growth hormone stimulation test).
- IGF-1 (also called Somatomedin-C)
- Bone age
  - Predictable change in size, shape, ossification, and closure of epiphyses
  - Left wrist
  - Most accurate after age 2 years
- Karyotype
- Consider MRI of CNS, with focus on sella turcica
- Growth Hormone Stimulation test
Let’s now return to our patients….

Practice Case 1:
A 9 year-old boy comes to clinic for a camp physical exam and his father notes that he has not grown very much this past year. On review of his record you confirm this. You note that on his growth curve at 7 years of age he was at the 25th percentile for height, at age 8 he was just above the 10th percentile and now he is below the 10th percentile for height. Yet, he has been gaining weight appropriately and is at the 10th percentile for age.

This patient has only gained 10cm of height over the last 3 years. A height gain of less than 5 cm/year, at any age, is abnormal. His growth curve also reveals normal weight gain, with only his height being affected. With this degree of height abnormality, and a normal weight gain pattern, intestinal abnormalities such as inflammatory bowel disease are very unlikely. The growth pattern is most consistent with an endocrine deficiency such as growth hormone or thyroid hormone deficiency, or both.

Upon further inquiry you find out that he is otherwise healthy, not on any medications, and has negative Review of Systems. His physical exam is remarkable for him appearing younger than his stated age and having short stature. Otherwise, there are no midline defects, no murmurs, and he has a normal neurologic exam. Further his TV is 2ml and he has no pubic hair.

Initial blood work revealed normal CBC, ESR, and CMP. His thyroid function tests were normal. His IGF-1 level was <25 which is low for his age. To evaluate him further, his bone age reveals that his skeletal maturation is delayed more than expected for his age. He undergoes an MRI of his brain and pituitary which were normal. Finally, he undergoes growth hormone stimulation testing with 2 agents both of which he failed.

He was diagnosed with isolated GHD and was started on growth hormone injections. This was atypical presentation for isolated GHD which usually presents earlier in childhood. In 6 months, his growth velocity had improved to 6 cm/yr on relatively low doses of GH.

In conclusion, growth failure is a symptom of underlying disease/disorder which needs to be elucidated. It is important to find the cause and remedy it, so there are no detrimental effects on growth and in certain cases, development.

Practice Case 2:
A 3 year-old male comes to your clinic as a follow-up appointment from the pediatric ward. You find that the child was admitted for 5 days for an “asthma flare.” You discover that the child has been hospitalized four times in his life beginning at age 9 months for “wheezing” episodes. You plot today’s height and weight in the growth chart of the electronic medical record and notice that he is 25th percentile for height, but now <5th percentile for weight. You wonder if anyone else has noticed that he has fallen off the growth curve. Could this patient have an underlying treatable condition?
During your history taking with the parents, you find that the child was born full term with an unremarkable prenatal course, spontaneous vaginal delivery, and newborn course. In addition to being seen in clinic for trouble breathing associated with wheezing, he has also been treated with antibiotics on several occasions for sinus infections as an outpatient. He has met all of his developmental milestones at his well-child visits. During your Review of Systems, you find that he has had an intermittent cough for many months. When you ask about his weight, his parents state that he has always been “skinny,” despite “eating all the time.” On physical exam, you notice that he has digital clubbing on both hands and has scattered wheezes on lung exam. Due to recurrent sinopulmonary infections and your suspicion for a malabsorption syndrome, you send a sweat chloride test, which comes back elevated and confirms the diagnosis of cystic fibrosis.

Practice Questions:
1. The most common cause of growth failure is:
   a. growth hormone deficiency
   b. chronic malnutrition
   c. thyroid hormone deficiency
   d. chronic disease
2. The most common finding in girls with Turner syndrome is:
   a. bicuspid aortic arch
   b. shield chest
   c. short stature
   d. low posterior hair-line
3. Constitutional Delay of Growth and Puberty is not associated with a delay in bone age (skeletal maturation). True or False?
4. After what age is crossing percentile lines considered abnormal?
   a. 6 months
   b. 12 months
   c. 24 months
   d. 36 months
5. The start of puberty is often manifested with breast development in females and with axillary hair growth in males. True or False?
6. You are currently assisting several pediatricians with a humanitarian mission in a resource poor country and encounter several children who are malnourished. Which of the following growth parameters will most likely be affected first in a child who is not meeting the proper caloric intake?
   a. Height
   b. Weight
   c. Head circumference
Answers to Practice Questions:

1. B. Worldwide and domestically, malnutrition remains the most common cause of growth failure. Remember these children have the typical pattern of weight falling off the curve before height and finally head circumference.

2. C. Phenotypic features may be subtle or absent, while short-stature is a cardinal feature of this condition. They can have a shield-like chest, webbing of the neck, and heart conditions (most commonly coarctation of the aorta and bicuspid aortic valve).

3. False. In children with Constitutional Delay of Growth and Puberty, or the ‘late bloomers,’ puberty, pubertal growth spurt, and bone age are all delayed and there is often a family history of ‘late bloomers.’

4. C. Children may cross height or weight percentile lines in the first 2 years of life as determined by intrauterine factors and genetic factors. However, after 24 months this would be considered abnormal and require a thorough investigation.

5. False. Puberty begins with enlarging testicular volume in boys.

6. B. In cases of malnutrition, weight is the first growth parameter to be affected, followed by height, and then head circumference.
ICR Growth Disorders: Small Group Case Studies

CASE 1

A 13 year-old boy comes to your clinic asking for referral for growth hormone therapy. You note that his height has always been below the 5th percentile for age, but has grown parallel to the curve. The growth curve is enclosed. This has begun to increasingly bother him and he wants to be treated.

On further history, he has been remarkably healthy and his Review of Systems is completely normal. He was a term baby weighing 7 lbs 4oz, and his height gradually went from the 50th percentile at birth to the 5th percentile by age 3. Since that time he has grown parallel to and just below the 5th percentile curve.

His father is 5’8” and his mother is 5’3”.

Do you think that he needs to be evaluated? If so, how would you start?

Is he growth hormone deficient?

Would growth hormone therapy be useful for him?

CASE 2

An 8½ year-old African American girl is referred to you for evaluation of possible Cushing syndrome. Her primary care physician was concerned about her rapid weight gain and “moon facies.” She started gaining weight rapidly at age 5½ and her weight is now greater than the 97th percentile and her height is at the 97th percentile. The growth curve is enclosed. On physical exam, she has diffuse obesity, with striae over her mid-section and upper thighs.

What is her chief complaint?

What additional history would be useful?
What physical exam findings are important?

What is the Differential Diagnosis?

Do you want any lab tests?

Does she have Cushing syndrome?

CASE 3

A 13 year-old girl is referred to you for short stature. Review of her growth chart shows growth along the 25th percentile for height up until age 3 and then a gradual fall to less than the 3rd percentile by age 5 years. The growth curve is enclosed. Her mother is 5ft 6in, had menarche at 12 years of age, and her father is 5ft 10in with no growth after high school. She has no complaints on review of symptoms. On physical exam, she is short with early breast budding and no pubic hair. The remainder of her exam is unremarkable.

Is this a normal growth pattern?

Does our patient have delayed puberty?

What is her expected growth percentile range based on her parents’ height?

What evaluation (i.e. lab and/or radiologic tests) would you perform?
Questions:
1. What other questions should you ask?
2. What is important to assess on physical examination?
3. What additional laboratory tests should you obtain?
4. What causes of her fever should you consider?
5. Should you make some changes in her management?

Objectives:
Following the lecture and small group discussion sessions the student should:
1) Understand the definition of fever and differences in temperature values with sites used for measurement
2) Understand the rational work up for fever (history, physical examination, labs to consider)
   - Know an approach to the evaluation and initial management of fever in a pediatric population and how it contrasts from evaluation in an adult or elderly individual.
3) Know the pathogenesis of fever and causes of an attenuated fever response
4) List common “false positive” causes of temperature elevation (i.e. smoking, mastication)
5) List the common causes of a pulse/temperature dissociation (relative bradycardia)
6) List supportive care/treatment for fever to include when to consider empiric treatment of fever
   (i.e. groups where elevated temperature harmful--patients with coronary artery disease or febrile seizures)
7) Understand the potential emergent nature of fever in neonates

Overview
Temperature is one of the vital signs. Therefore, recognizing the presence of a fever and being able to generate a prioritized differential diagnosis for this physical finding is essential for your future success as a physician. This section will review definitions, pathogenesis, modes of measurement (and limitations), and a rational diagnostic approach to a patient with a fever. Fever is a key finding. Considerations of fever in a special population (children) will be discussed in the latter half. This section will also employ heuristics (rules of thumb), and pattern recognition (basic illness scripts).

Definitions
What is fever? According to the International Union of Physiological Sciences Commission for Thermal Physiology, fever is “a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of
live (micro-organisms) or inanimate matter recognized as pathogenic or alien by the host.” [1] In a practical sense, fever is the elevation of core body temperature above the normal daily variations as a result of pyrogenic cytokine’s effect on the hypothalamic center.

Hyperthermia is not the same as fever. Hyperthermia is an unregulated rise in body temperature not due to a direct effect of pyrogenic cytokines. Antipyretics such as acetaminophen or ibuprofen are generally not effective in hyperthermia. Hyperthermia is due to impaired thermoregulatory homeostasis (an unchanged thermoregulatory center setting) with either too little heat dissipation, too much heat production, or inappropriate thermoregulation. Examples of hyperthermia are heat stroke, drug related hyperthermia (cocaine, ecstasy, anticholinergics), neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia associated with some anesthetics, thyrotoxicosis, pheochromocytoma, and central nervous system damage. Temperatures over 41.5°C (>106.7°F) are called hyperpyrexia.

The febrile response is more than a temperature rise. Fever is a “complex physiologic response involving not only cytokine-mediated increase in core body temperature but also the generation of acute phase reactants (APRs) and activation of many immunologic, physiologic and endocrinologic systems”.[2] The febrile response is stimulated by an infectious or inflammatory trigger. As the immune system encounters an infectious agent, immune cells are activated and start producing cytokines. Some cytokines, such as IL-6, are pyrogenic and also stimulate production of APRs that may cause physiologic responses manifested by the individual as headache, somnolence, anorexia or myalgias. They can alter hematologic and coagulation parameters, hormone synthesis. The effects of inflammatory cytokines, especially over a number of days or weeks, may be demonstrated in laboratory findings such as an elevated erythrocyte sedimentation rate (ESR), C reactive protein (CRP), haptoglobin, ferritin and fibrinogen. Infections nearly always cause changes in the white blood cell count and differential but cytokines are also responsible for mild anemia and/or thrombocytosis. Effects on the liver can decrease the production of clotting factors, albumin, transferrin and thyroxine binding globulin. Some of these APRs, particularly the ESR and CRP, may be followed to demonstrate changes of an inflammatory state.

Fever of unknown origin (FUO) is a term that is often misused in medicine. FUO is NOT fever in a patient who presents with no demonstrable source of infection but classical FUO is defined as “a temperature greater than 38.3°C on several occasions, with duration of fever for 3 weeks or more, with uncertain diagnosis after one week of investigation in the hospital or upon equivalent outpatient evaluation”. [3]

The pathogenesis of fever

The preoptic area of the hypothalamus controls body temperature. Neurons in the anterior and posterior hypothalamus receive signals from the temperature of the blood and from temperature receptors on peripheral nerves. These signals are processed by the thermoregulatory center of the hypothalamus to maintain a normal range of body temperature. This center balances excess heat production from metabolic activity with heat dissipation from the skin and airways/lungs. Fever producing substances include endogenous pyrogens (derived from host cells) such as cytokines and exogenous pyrogens (produced outside the body) such as micro-
organisms, microbial toxins, endotoxin, and mediators of inflammation. The so-called pro-
inflammatory or pyrogenic cytokines include interleukin-1 (IL-1), IL-6, tumor necrosis factor
alpha (TNF-α), interferon gamma (IFN-γ), and ciliary neurotropic factor (CNF). These interact
with their receptors in the preoptic region of the anterior region of the hypothalamus resulting in
activation of phospholipase A₂. This releases plasma membrane arachidonic acid (a substrate for
the cyclo-oxygenase pathway). Arachidonate metabolite PGE₂ may be the local mediator that
activates thermosensitive neurons. Heat is produced by shivering (increased metabolic activity
in the muscles) and vasoconstriction shunts warm blood from the skin. In an effort to reduce
heat, the body sweats and vasodilates.

**What is a normal temperature?**

In adults, because of individual variability, no single temperature can be considered the upper
limit of normal but it is generally accepted that temperature readings above
38-38.2°C (100.4-100.8 °F) suggest fever. A landmark study in healthy young, primarily African
American males in Baltimore, Maryland, using an oral electronic thermometer, found a mean
oral temperature of 98.2 ± 0.7 °F with a nadir at 0600 and daily peaks at
1600-1800 hours. Overall, females had a slightly higher average temperature than males. [4] A
systematic review of articles published between 1939 and 1990 identified the range for oral
temperature in normal adults to be 33.2-38.2°C. [5] So where did the “normal is 98.6°F” come
from? We have to go back to 1868, when Carl Reinhold August Wunderlich published “The
course of temperature in disease”, in which he reported that the mean temperature of healthy
adults is 98.6°F. Using a large glass mercury thermometer placed in the axilla, he measured
several million temperatures in more than 25,000 people, thereby providing one of the first
quantitative definitions of fever. Recent tests of one of his thermometers (College of Physicians
Museum, Philadelphia, PA) found it read 1.4-2.2°C higher than current instruments. [6]
Normal temperature ranges in children have not been systematically studied. It has been
suggested that temperature is higher in infants, decreases by 1 year of age, and stabilizes by 13-
14 years old in girls and 17-18 years in boys. [7]

**Measurement of Temperature**

The measurement of core temperatures is too invasive to be routinely done. Core temperature
is best measured in the right atrium or pulmonary artery.

The formula to convert degrees F to degrees C is:

\[
\text{Temp } C = \frac{(\text{Temp } F - 32)}{1.8}
\]

The formula to convert degrees C to degrees F is:

\[
\text{Temp } F = (\text{Temp } C \times 1.8) + 32
\]

The body has many different temperatures representative of each particular body part. It is
recommended that mixing and matching temperatures from various sites be interpreted with
cautions. All methods of measuring body temperature have limitations. Rectal temperatures are
usually higher than other sites but stool in the rectum may delay or decrease temperature
measurement if the thermometer is directly inserted into it. In young children, this remains the preferred method of measuring core body temperature. During shock there is poor rectal perfusion which may result in a low reading. Oral temperatures are usually preferred but correct positioning in the sublingual pocket is needed. Oral readings may vary 1.7°F between the rear sublingual pocket and the anterior floor of the mouth below the frenulum. [8]

Oral temperatures require patient cooperation, and can change if the mouth is open or closed. Smoking and vigorous chewing may increase oral temperatures for 20 minutes, cold drinks and mouth breathing during cold weather can decrease oral temperatures for 10 minutes. [9]

Tympanic membrane (TM) temperatures are easy to measure. The TM is perfused by a tributary of the common carotid artery that perfuses the thermoregulatory center, so theoretically this should be a good site to sample. There are many different types of infrared TM thermometers and they have highly variable readings. They are difficult to use in children less than one year of age. They may read falsely low if the seal in the ear canal is poor, and should not be used if blood or purulent discharge is present in the ear. Ear wax can decrease temperature measurements and chewing gum has been reported to increase TM readings. [10,11]

Axillary temperatures in the neonate (mercury thermometer in place for 5 minutes) seem to approximate the core temperature but are not accurate in the older child or adult. Monitoring skin temperature with plastic strips with implanted temperature sensitive crystals is a relatively insensitive measure. Two studies addressed the ability to tactilely detect temperature elevations. Nursing assistant’s palpation of the skin on the forehead identified 42% of 138 patients with temperatures >38°C; 1.8% of > 1000 afebrile children were judged febrile. [12] Mothers had a 73.9% sensitivity and 85% specificity for detecting fever in their child when their temperature was >38°C. [13]

Finally, temporal artery (TA) scanning has been touted as the newest technology that can help monitor patient temperatures. While many scanners are commercially available to patients and healthcare providers, there is a not a great deal of data on the utility of these in the healthcare setting. One study in the nursing literature noted that there is a difference between TA thermometry and rectal temperatures in children aged 3 to 36 months of age. [14] (.) They found that TA had only a sensitivity of 0.70 relative to the rectal method in detecting febrile children. Another study in adult trauma patients found that TA scanning differed by 1°F when compared to oral thermometry. Furthermore, it varied by body mass index much more than any other method. [15] Needless to say, the ease of using this technology has been sought in busy settings such as the emergency department. Two small studies differ on the utility of the technology in measuring fevers in children. One study in children aged 2 to 12 years of age found that TA readings correlated best with rectal temperature readings. [16] Conversely, another study in 3 to 36 month old children indicated that the TA method was only 53% sensitive at detecting a rectal temperature of 100.4°F and 27% sensitive at detecting a rectal temperature of 102.2°F. [17]

Besides anatomic variability in the measurement of temperature and limitations of equipment there are also physiologic variants. Recent research in healthy older subjects (mean age 80 years) has challenged prior teaching, finding that the healthy elderly average core temperature was no lower than healthy younger subjects (note that average oral and axillary readings were found to be lower but comparable rectal temperatures). [18] Systematic review found two well-designed studies, with one reporting that teething is unlikely to be associated with fever, and the other suggesting that the temperature is modestly increased (37.3°C to 37.9°C) at the time of first tooth eruption. [19,20] There is no evidence that teething causes a
temperature elevation into the febrile range. Bundling and a warm environment can increase newborn rectal temperatures into the fever range. [21] Females’ temperatures increase an average of 0.5°C (0.9°F) at the time of ovulation.[22] Psychiatric illness (such as chronic depression) has been associated with altered thermoregulation. Working the night shift or other reversals of the usual sleep-wake cycle have been associated with temperature zenith in the early afternoon and nadir in the early morning. Attenuated febrile responses have been associated with the following conditions: newborn status, uremia, cirrhosis, use of antipyretics, corticosteroids, large burns, and extracorporeal membrane oxygenation.

As you arrive to evaluate the febrile patient her nurse wants to know if she should administer acetaminophen and change antibiotics commenting “this woman has been febrile since admission and nothing has been done for this.” The patient’s repeat oral temperature when you arrive is 38.8 °C (101.9 °F). She complains of “feeling a bit chilly” and exam reveals mild right-sided costovertebral tenderness that the patient expresses is much improved from when she arrived. Do you need to give antipyretics? Are there any dangers in this patient having a fever? Are there any disadvantages in giving antipyretics like acetaminophen, aspirin or ibuprofen? Has she “failed antibiotics” and does she need them changed?

When is fever harmful?

Temperature > 41.5°C (106°F) is called hyperpyrexia. It is known that in heat stroke humans have widespread organ dysfunction at body temperatures > 41°C (105°F). The average lethal limit of temperature in humans is 43°C (109°F). Dubois studied 357 febrile patients with pneumonia, relapsing fever (borrelial infection), or malaria and he found that in patients with infection that fever was rarely > 40°C (105°F). [23]

There are metabolic consequences to fever. The heart rate generally increases 2.4 beats/minute for each 1°F rise in body temperature. [9] For every 1°C above 37°C, there is an estimated 13% increase in oxygen consumption. [24] As a result, there are medical conditions when decreasing the fever is recommended: specifically cardiovascular and pulmonary disease where the metabolic cost of increased sympathetic tone, oxygen consumption, increased respiratory minute volume and increased respiratory quotient would be poorly tolerated. However, one should recall that in coronary artery disease (CAD) indomethacin has been associated with vasoconstriction in those with significant CAD and more recently the COX-2 selective nonsteroidal anti-inflammatory agents have also been associated with an increase in coronary thrombosis and risk of death. [25] Another patient population where control of fever is advanced are those with organic brain disorder when fever may cause further alterations in mental status. It should be noted that there are no reports of brain injury caused by fever from infection in a previously normal person. The last area of consideration is children and febrile seizures. In children ages 3 months to 5 years, 2-14 % have febrile seizures, most when the temperature is > 102°F. [26] In a randomized controlled trial of febrile seizures, treatment with phenobarbital and antipyretics was associated with a recurrence rate of 5%, versus 25% in the placebo and antipyretics arm. [27] In another study, acetaminophen failed to reduce the rate of febrile seizures. [28]

Is fever beneficial?

29:5
Fever in response to infection is seen in all mammals, and even cold-blooded reptiles with infections have been observed to move into sunny areas to raise their body temperature. Clearly, there is an evolutionary advantage to the febrile response that has been maintained for millions of years. In reptile studies there is a direct connection between increased body temperature and survival during *Aeromonas* infection, with increased mortality occurring with the administration of sodium salicylate.[29] In 218 patients with gram negative bacteremia, maximal temperature at the time of the documented bacteremia positively correlated with subsequent survival.[30] In spontaneous bacterial peritonitis, temperature > 100.4°F was positively correlated with survival. [31] Children with chickenpox receiving acetaminophen showed a longer time of total lesion crusting than placebo. [32] In a placebo controlled study of adults with rhinovirus infection (common cold), more had longer viral shedding when given aspirin. [33] In influenza A infection, a relationship between antipyretic use and prolonged illness has been noted. [34] In aggregate, these studies suggest that fever is an important body defense mechanism that contributes to the host’s ability to resist infection.

**Patterns of fever**

The classically described patterns of fever are interesting and occasionally of value in diagnosis, especially in resource limited circumstances and diagnostic dilemmas. However, it should be acknowledged that these patterns were generally described in the pre-antibiotic period, and are less applicable in the modern era of sophisticated imagery, broad spectrum antimicrobials, and frequent temperature manipulation with antipyretics. Pulse temperature dissociations are conditions where the heart rate does not appropriately increase with fever. On your differential diagnosis of this “relative bradycardia” are the following conditions: Typhoid fever, Brucellosis, Dengue, Q fever, Leptospirosis, Legionellosis, Psittacosis, Typhus, Sand Fly Fever, Rocky Mountain Spotted Fever, Malaria, Yellow Fever, Babesiosis, some drug fevers, factitious fever, lymphoma, central nervous system lesions and pseudo-pulse dissociation (such as use of beta blockers). Continuous fever is associated with few remissions that last more than 2 hours. A classic example is *Salmonella* infections including typhoid fever. Intermittent, hectic picket fence, or quotidian fever, is associated with wide up and down fluctuations. A classical example of the intermittent fever pattern is associated with an abscess. Tertian (every three days) and Quartan fever (every fourth day) are generally associated with chronic malaria infection. Saddleback fevers are fevers of several days, followed by defervescence for a few days, then recurrence of fever. Dengue fever is the usual example given. Pel-Ebstein fever patterns are long periods (week or greater) with equally long or longer periods of defervescence, then recurrence. This is the pattern generally described with Hodgkin’s lymphoma. In a study at a Veteran’s Affairs Medical Center, 404 patients with 102 fevers were studied. There was no diagnostic relationship evident with various patterns of fever. Intermittent fevers, most with diurnal variation, predominated but in most cases the authors reported that there was not enough data present (short admissions/interventions) to determine a pattern. This study concluded that in the modern era fever patterns are unlikely to be diagnostic.[35] Finally, a group of likely inheritable periodic fever syndromes exist. The most common of these in children is the PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis) syndrome. In this syndrome, children present in childhood with cyclical fever normally from 21-35 days apart. The exact etiology remains unsolved but the syndrome is self-resolving. Other diseases in this differential include Familial Mediterranean Fever, TRAPS (TNF Receptor-Associated Periodic Fever) and Hyper-IgD syndrome (HIDS). [36]
**Differential diagnosis of fever**

Few signs and symptoms in medicine have as many diagnostic possibilities as fever (Table 1). All fever is not related to infection. Fever is often associated with inflammatory conditions where pyrogenic cytokines are likely released.

**Clinical approaches to the febrile patient**

A meticulous history is critical in determining the cause of fever. The chronology of symptoms and relationship to procedures; preventive measures, prosthetic devices, and medications are important to develop. Underlying host characteristics, occupational exposure, geographic and travel exposures can be most helpful. Usual and unusual hobbies including swimming, hot tubbing, caving, safari, and animal contact are useful to discuss. Personal practices including diet (especially unpasteurized milk, organic products, rare or raw meat, eggs, fish) and sexual exposures should be probed. Pets, bites, arthropod assault, immunizations (especially in children) and medications are important. A complete and often repeated physical examination is essential. All vital signs are relevant. The systemic inflammatory response syndrome (SIRS) is characterized by temperature > 38°C or < 36°C, heart rate > 90 beats/minute, respiratory rate > 20 breaths/minute or PaCO₂ < 32 and white blood cell count > 12,000 or < 4,000, or > 10% band forms. The syndrome suggests a higher level of severity for the patient’s condition. Temperature should be consistently measured at the same site. The skin and mucous membranes should carefully be visualized for vesicles, petechiae or purpura (suggesting need for isolation initially) and the coughing febrile patient may benefit from wearing a mask until the evaluation is more mature. On physical examination the patient’s appearance is very important - do they look sick or not? This drives the tempo of immediate diagnostic and therapeutic actions. In the physical examination, mental status, eyes, nail beds, lymph nodes, skin, heart, chest, abdomen (including hepatosplenomegaly), neck stiffness, catheter sites, rectal, pelvic areas should all be evaluated with particular care.

If your assessment is that patient has more than a simple localized infection (e.g., streptococcal pharyngitis) or a viral infection, then additional laboratory and imaging studies should be ordered. Sutton’s Law (go where the money is) - or in this case where the symptoms and signs localize to - should inform your subsequent workup. In general, febrile patients should have a complete blood count with differential (clues like bacterial infection often shows increased band forms, some parasitic infections show high eosinophils, viral infections atypical lymphocytes). Any febrile patient with travel history to endemic region or recent blood transfusion should have malaria and Babesia blood smears/rapid tests performed. Urinalysis, sampling any abnormal fluid collection (e.g., joint fluid, pleural, pericardial, peritoneal fluid), and culture of blood, urine, abnormal fluid collections, sputum if cough are recommended. Blood chemistries including liver associated enzymes, renal function, electrolytes, and glucose should be performed. A chest radiograph is indicated. If there are symptoms or signs of central nervous system involvement then a lumbar puncture to facilitate the analysis of cerebrospinal fluid should be considered. Overall, these lab tests focus on identifying common infectious causes but one must remember that the differential of fever is very broad and often non-infectious. The patient’s history and your diagnostic skills may lead you to look for other etiologies such as pulmonary embolus, vasculitis, drug fever, and neoplasm.
In the febrile patient, your periodic reassessment may identify concerning findings indicative of progression of the illness. Such harbingers include hypotension, tachycardia, respiratory distress, altered mental status, decreased urine output (oliguria or anuria), bleeding (disseminated intravascular coagulation), and lactic acidosis. Under such circumstances, one does not have the luxury of following the preferred approach of first identifying a diagnosis/then proceeding with targeted treatment. In critically ill febrile patients, it is imperative to conduct a rapid assessment, including collection of diagnostic samples for microbiology, followed by empiric antibiotics and resuscitation. When possible, you should then adjust your therapy more specifically as the results of cultures and other diagnostic tests return.

At the bedside of a febrile elderly woman who was hospitalized 36 hours ago, in addition to determining the etiology of the fever, you are concerned about what effects the fever may have on the patient, especially the potential impact that increased oxygen demands and stress may have on underlying coronary artery disease or dysrhythmias.

You note that the patient has a blood pressure of 114/82, a pulse of 92, a normal electrocardiogram and no history of heart disease. A review of her fever curve reveals that her temperature has ranged from a peak of 103.4°F at the time of admission, to a low of 100.6°F about six hours ago. Thus, while her temperature has decreased, she has not been afebrile since admission. Recognizing that a great deal of the discomfort associated with fever is actually with the chills and sweats associated with rise and fall of temperature and that there is some benefit to the febrile response, you elect not to give her antipyretics at this time.

You then turn to the question of the impact of antibiotic therapy – should this patient be afebrile after 36 hours of appropriate antibiotics? You also note that on admission she had a white blood cell count (WBC) of 19,700 including 74% neutrophils and 4% band forms, very purulent urine with >500 WBCs per high powered field and a urine Gram’s stain with numerous Gram negative rods. She received her first dose of levofloxacin in the emergency room and has received two subsequent doses as ordered. The urine culture and sensitivity will be available tomorrow.

In organizing your thoughts you put together a brief problem list to ensure that you are considering all the relevant issues:

1. Persistent fever
2. Leukocytosis
3. Pyuria
4. Gram negative bacteruria
5. Advanced age

Appreciating that pyelonephritis is a serious infection that can be associated with bacteremia and formation of an abscess, you consider whether further imaging is needed or whether a resistant organism could be involved. You also understand that antibiotics do not instantly eradicate an infection and the tissue inflammation associated with a renal infection. Since you have determined that the patient’s fever is decreasing and that her WBC had declined to 9,900 today, you correctly conclude that there has been an appropriate response to antibiotics and elect not to change therapy at this time. In the chart you note that you will check the culture results in the morning to ensure that there is not a resistant organism present and that you will consider diagnostic imaging looking for a renal abscess if the patient remains febrile at 72 hours after admission.
You explain your reasoning to the patient and nursing staff and add that you will be back in a few hours to see how she is doing.

**When should you treat fever (the physical sign)?**

Generally, the preferred approach is to address and treat the underlying cause of the fever, not symptomatically reduce the fever. Many fevers are self-limited, often associated with viral infections. There is no evidence base to definitively determine whether patients truly have improved comfort from the use of antipyratics. However, the short-term use of antipyratics is associated with very little risk. Aspirin should be avoided in young children due to the potential to induce Reyes syndrome. More broadly, there is also concern about potential toxicity (e.g., hepatotoxicity with acetaminophen, and gastrointestinal or renal toxicity with NSAIDs) of antipyratics, as well as some evidence that fever suppression may prolong the illness while reducing the intensity of symptoms. All commonly used antipyratics (aspirin, NSAIDS, acetaminophen) block the conversion of arachidonic acid to prostaglandins (such as PGE₂) by inhibiting cyclo-oxygenases. We have reviewed underlying medical conditions (cardiovascular, pulmonary, neurologic) where consideration may be given for the use of antipyratics to suppress the metabolic consequences of fever.

**Key points:**

- Fever is a physical finding (sign of elevated core body temperature).
- The mean normal temperature is 98.2 ± 0.7°F but there is a range of normal including variations based on time of day, gender, anatomic site measured, and host physiology.
- The febrile response includes fever, acute phase reactants, and cytokines with activation of inflammatory, immunologic, physiologic, and endocrine systems.
- There are medical conditions associated with attenuated febrile responses and there are medical conditions where fever may be harmful due to its metabolic consequences.
- Although all fever needs to be evaluated to determine its etiology, not all fever needs to be treated.
- All fever does not equate to being caused by infection, think broadly in your differential diagnosis.
- Never forget that some febrile patients can be contagious. Always be safer than sorry.
<table>
<thead>
<tr>
<th>Etiologies Causing Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Mechanical Trauma (crush injury)</td>
</tr>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>-lymphoma, liver metastases, hepatocellular carcinoma, renal cell carcinoma</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>-commonly penicillin, drugs with a sulfa moiety, quinidine, monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>- (cocaine, LSD, PCP, speed, ecstasy)</td>
</tr>
<tr>
<td>Central nervous system disorders</td>
</tr>
<tr>
<td>Acute hemolysis</td>
</tr>
<tr>
<td>Large vascular accident (stroke, myocardial infarction, pulmonary embolus)</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Malignant neuroleptic syndrome</td>
</tr>
<tr>
<td>Malignant hyperthermia (anesthetics)</td>
</tr>
<tr>
<td>Acute metabolic disorders</td>
</tr>
<tr>
<td>-Gout, porphyria, thyrotoxicosis, delirium tremens, pheochromocytoma, adrenal insufficiency</td>
</tr>
</tbody>
</table>
Your next patient (considerations in the pediatric population)

Your next patient, a 6 month old female presents with her parents with a chief complaint of a fever to 103.1°F. Her parents noted that when she awoke this morning she felt warm to them. Her mother attempted to nurse her but she did not feed well. Additionally, she vomited shortly after this feeding and another time while waiting in the Emergency Department. She seemed mildly irritable but was consolable when in her mother’s arms. They indicated that she went to bed the previous evening with no unusual occurrences. She has been previously well with no other febrile episodes. She has received her routine 2 and 4 month-old immunizations and is due for her 6 month-old immunizations. Her mother’s pregnancy was unremarkable. Her vital signs at the hospital are T – 103.5°F, Pulse – 160, RR – 18, BP – 88/52. Her physical examination is unremarkable with no neck stiffness, increased respiratory effort or abnormalities, abdominal tenderness or rashes noted.

What is your approach to this patient? Should laboratory or radiologic testing be completed? Should the child receive any therapies?

What does a fever clinically mean?

The presence of a fever may represent the onset of a systemic infection in children. Young children are relatively immunocompromised. Additionally, they may not have received their routine immunizations. For these reasons, they are at a greater risk for serious bacterial illnesses that may be initially manifested by fever. In children less than 3 years of age, the presence of fever is associated with an increased risk of bacteremia, sepsis and other serious bacterial infections such as urinary tract infections or meningitis.

We will look at these children in two different groups, <3 months and 3 months-3 years of age.

Fever in children less than 3 months of age

Children with fever in this age group are at increased risk for bacterial illness. While most febrile illnesses are still due to the most common viral pathogens, children must be thoroughly assessed for bacterial pathogens. In this age group, it is sometimes difficult for the most astute physicians to find outward signs and symptoms of serious illness. Often times, fever associated with subtle changes in feeding and sleeping patterns may be the only findings reported by parents and physicians. Undiagnosed bacterial illnesses may have devastating results. For that reason, laboratory and possibly radiologic evaluation are nearly always added to the routine history and physical performed by the provider. Additionally, many children < 1 to 2 months of age are routinely admitted to the hospital and started on antibiotics while the laboratory assessments are allowed to be processed (24-48 hours).

The laboratory evaluation most commonly includes a complete blood count (CBC) with particular attention paid to the WBC (white blood cell) count, urinalysis, cerebrospinal fluid (CSF) analysis and cultures of all of these fluids. The CBC is often one of the first and most important pieces of information. Most studies have found that the WBC count is one of the best predictors of a bacterial infection. Most practitioners are concerned when the WBC is either < 5000 or > 15,000 WBC/µL.[37, 38] Either of these findings would prompt a greater concern for a bacterial infection with the greatest concern noted in children with extremely low WBC. The urinalysis is the best predictor of a urinary tract infection (UTI), the most common serious
bacterial infection in this age group. Specimens should be obtained by either the catheter or suprapubic methods in order to ensure sterility of the specimen. Urine that has the presence of leukocyte esterase or nitrite indicates the possible presence of bacteria. Additionally, microscopic examination of the urine may reveal the presence of WBC or bacteria. This examination may be enhanced with the addition of a Gram’s stain of the urine. Finally, the CSF analysis is done to assess for meningitis. Important parameters include the WBC count in the CSF, the protein and glucose levels and Gram’s stain of the fluid. It should be noted that the normal CSF values in children less than one month of age differ from the evaluation in nearly every other age group.

Radiologic examination is normally reserved only for those children who have evidence of respiratory disease. Tachypnea and mild difficulty breathing may be the only initial signs of pneumonia. While most pediatricians would not routinely get a chest x-ray on all children with fever, it is often considered in children with evidence of a possible infection.

There is one very serious viral infection that may be marked by the onset of fever in children less than one month of age. This is neonatal herpes simplex virus (HSV) infection. This infection may have many manifestations to include skin and mucous membrane findings, meningoencephalitis and or disseminated disease that appears as sepsis. Most cases will present between one and three weeks of age. Many institutions will include evaluation for HSV in children presenting with fever less than one month of age and abnormal laboratory results or a rash suggestive of HSV. This evaluation normally consists of adding HSV polymerase chain reaction testing to abnormal CSF and culturing or doing other specific HSV testing (direct fluorescent antibody test, DFA, or Tzanck smear) of suspicious lesions. Treatment would include the addition of intravenous acyclovir in addition to empiric antibacterials while the laboratory tests are processed.

**Fever in children between 3 months and 3 years of age**

Children in this age group who have a febrile illness most commonly have viral illnesses that they have contracted from family members, care givers or day care settings. It is less common than the previous group for them to have invasive bacterial illnesses. In some cases, their fever may represent the first sign of an entity referred to as occult bacteremia. Essentially, this is bacteremia without any identifiable focus. Historically, the bacteremia has been associated with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type B.

In studies in the 1980’s, nearly 8% of children with fever to 103°F and an elevated WBC count were noted to have bacteremia.[39] Recent advances in childhood immunizations have led to a decrease in the rate of such infections to around 1% in similar children.[40,41] (While the evaluation of such children is somewhat easier, fever may be the only signal that a more serious illness is impending. Practitioners are able to determine how these children interact with their parents, their environment and respond to stimuli. These assessments make it easier to rule out diagnoses such as meningitis but may not be useful to determine if a child has bacteremia or a urinary tract infection. Therefore, these children often have a laboratory evaluation unless history and physical exam reveal findings consistent with a diagnosis such as otitis media or gastroenteritis.
Laboratory evaluation in these patients most often includes only a complete blood count (CBC) and a urinalysis, with cultures of the blood and urine if necessary. Urinary tract infections (UTI) are the most common etiology found to be associated with febrile illnesses. Most specimens will still be collected by catheterization but some older children may be able to provide a clean catch specimen. Children with anatomic abnormalities of the urinary tract (such as vesicoureteral reflux) are at very high risk for UTI. A febrile illness due to a UTI may be the only suggestion that such abnormalities exist. Once again, a white blood cell (WBC) count in the peripheral blood of > 15,000/uL is suggestive for bacteremia. If diarrhea is present, stool can be evaluated for possible bacterial etiologies although rapid assessment for stool leukocytes is not commonly performed in many healthcare facilities. Finally, chest x-rays as discussed above are also utilized to help assess children with fevers and respiratory symptoms who may have a lower respiratory tract infection.

The significance of “occult” bacteremia is somewhat debated. Most children who have normal immune systems are capable of clearing the bacteremia without suppurative complications. On the other hand, some of these episodes likely spread distally and result in infections such as osteomyelitis, pneumonia and meningitis. For this reason, children who meet high-risk criteria (elevated WBC) often receive empiric antibiotics while their blood and urine cultures are pending. If a blood culture is positive for a pathogen, then the children must be assessed very thoroughly to insure that no disseminated disease has been noted. Children with abnormal urinalysis need to be treated for a urinary tract infection. Parenteral therapy is indicated for very small children, those who cannot tolerate oral medicine and those at risk for serious urinary tract infections such as pyelonephritis.

**Microbes and Therapy**

In the evaluation of small children with fever, empiric antibiotics are often started in order to treat for the most common pathogens while laboratory tests are run to confirm the proper diagnosis. Tables 2 and 3 provide a guideline for the choice of initial antimicrobials for children under the age of three years who have a febrile illness concerning for bacterial illness. Of note, these antimicrobials are most often given parenterally (IV) while the results of cultures are pending.

The most commonly used antimicrobials in children belong to the penicillin, cephalosporin and aminoglycoside classes. As demonstrated in the Tables, the combination of these drugs provides broad-spectrum coverage versus most bacterial pathogens to include those implicated in fever and bacteremia, meningitis and urinary tract infections. By using a combination of these antimicrobials while waiting culture results, children can receive empiric therapy that should halt the progression of problems should the fever be associated with a bacterial pathogen.

The risks for certain pathogens may also depend upon the routine care that the children have been receiving. For instance, children in the United States regularly receive immunizations that protect them against *Haemophilus influenzae* type B and *Streptococcus pneumoniae*. By 6 months of life, they should have protective antibody levels against each of these pathogens if immunized. The result of such immunizations is that the rate of bacteremia in children with fever less than 3 months of age decreases from 8% to 1%. In fact, very little invasive disease is attributed to *Haemophilus influenzae* type B in the United States today when it was the most
common invasive bacterial pathogen in 1985. Practitioners must remember that children throughout the world may not receive these vaccines. If a person is practicing a region where healthcare access is limited and sees a febrile child, they will not have received the benefits of such vaccines and would be at a higher risk for illness.

Special consideration should be noted for children with fevers less than one month. Many institutions will begin empiric parenteral acyclovir for children being evaluated for possible HSV infection. This drug has very good activity against both HSV-1 and -2 with few side effects. The gold standard for the diagnosis of HSV infection is not culture but polymerase chain reaction (PCR) testing of the CSF for HSV-1 and -2. [42]

Empiric antibiotics are continued in these scenarios until the cultures or PCR tests are negative. In most cases, the etiology of these fevers is a mild viral illness not a bacterial illness. This can normally be accomplished in 24-48 hours after the initial evaluation.

Table 2: Empiric Therapy in Children Ages < 2-3 months

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Fever (Bacteremia)</th>
<th>Meningitis</th>
<th>UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B Streptococcus</td>
<td>E. coli</td>
<td>Listeria monocytogenes</td>
<td>Group B Streptococcus</td>
</tr>
<tr>
<td>E. coli</td>
<td>Listeria monocytogenes</td>
<td>Other Gram-negative organisms</td>
<td>E. coli</td>
</tr>
<tr>
<td>Other Gram-negative organisms</td>
<td>Herpes Simplex Virus (&lt; 1 mo)</td>
<td>Other Gram-negative organisms</td>
<td>Other Gram-negative organisms</td>
</tr>
<tr>
<td>Ampicillin for Listeria/GBS</td>
<td>Ampicillin for Listeria/GBS</td>
<td>Ampicillin for HSV *</td>
<td>Acyclovir for HSV *</td>
</tr>
<tr>
<td>Aminoglycoside or 3rd Gen Cephalosporin (Gram -)</td>
<td>3rd Gen Cephalosporin (Gram – and GBS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir for HSV *</td>
<td>Acyclovir for HSV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Empiric Therapy in Children Ages 3-36 months

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Fever (Bacteremia)</th>
<th>Meningitis</th>
<th>UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Neisseria meningitidis</td>
<td>Streptococcus pneumoniae</td>
<td>E. coli</td>
</tr>
<tr>
<td>(Haemophilus influenzae type B)</td>
<td>Neisseria meningitidis</td>
<td>Neisseria meningitidis</td>
<td>Other Gram (-)</td>
</tr>
<tr>
<td></td>
<td>(Haemophilus influenzae type B</td>
<td>(Haemophilus influenzae type B</td>
<td>Enterococcus species</td>
</tr>
<tr>
<td>3rd Generation Cephalosporin</td>
<td>3rd Generation Cephalosporin + Vancomycin for resistant</td>
<td>3rd Generation Cephalosporin for Gram (-), may add</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumoniae</td>
<td></td>
<td>ampicillin for Enterococcus sp.</td>
</tr>
</tbody>
</table>

Back to our second patient…
You decide that it is appropriate to embark on a laboratory evaluation. You order a complete blood count with a white blood cell differential, a urinalysis with a urine culture (which is obtained via an in and out catheterization procedure). You forego obtaining a chest x-ray or lumbar puncture based on the lack of associated signs and symptoms for pneumonia or meningitis respectively.

The complete blood count reveals a WBC of 17,800 WBC/mm³ with normal hemoglobin, hematocrit and platelets. The urinalysis (microscopic and dipstick) shows 50 WBC/HPF, 1+ bacteria, leukocyte esterase and nitrite tests were positive. Based on this information, you interpret that she has a urinary tract infection as the source of her fever. Based on her previous history of vomiting, you choose to administer an IV dose of ceftriaxone (3rd generation cephalosporin) and admit her to the hospital for close observation. The following day, her urine culture grows > 10⁶ colony forming units of a Gram-negative organism, Escherichia coli. Your patient defervesced and was discharged on an oral 3rd generation cephalosporin to receive further evaluation as an outpatient.
Practice Questions and Answers
1. Which ONE of the following is MOST CORRECT regarding body temperature and fever?
   A. Determining the pattern of a fever is essential in establishing its etiology
   B. Rapidly diminishing a fever should be the goal in most cases
   C. Fever from infectious causes is associated with a more elevated temperature than fever from non-infectious causes
   D. Temperature elevations associated with heat stroke have a different pathophysiology than temperature elevation associated with infection
   E. Regulation of core body temperature occurs in the pineal gland

2. A 1-month-old infant presents to the emergency room with a history of decreased eating and increased somnolence. Her temperature is 102.3°F. Which of the following laboratory tests would NOT be indicated in the evaluation of an infant for a serious infection?
   A. Complete blood count (CBC)
   B. Blood culture
   C. Blood Urea Nitrogen and Creatinine (BUN/CREAT)
   D. Urinalysis with microscopic examination (UA)

3. A two-week old newborn is noted to have a peripheral blood WBC of 3,600 white blood cells/mm³ and a lumbar puncture notable for 394 white blood cells/mm³ and 50 red blood cells/mm³.
   Which of the following pathogens is UNLIKELY to be the etiologic agent of this child’s illness?
   A. Herpes Simplex Virus
   B. Staphylococcus aureus
   C. Group B Streptococcus
   D. Escherichia coli

4. A 2-month-old female presents to the emergency room with a fever to 101.8°F. She has no symptoms suggestive of a respiratory tract infection or a gastrointestinal infection. All of her immunizations are up to date. Her physical examination is unremarkable except she is a bit uncomfortable.
   Which laboratory test below would be useful in diagnosing the most common bacterial infection in this child?
   A. Lumbar puncture
   B. Blood chemistry
   C. Chest x-ray
   D. Urinalysis

5. A 19 year old Army recruit comes to the emergency room for a new severe headache for one day. He is very ill-appearing and noted to have a temperature of 38 degrees C and a petechial rash on his lower extremities. Which of the following statements is MOST CORRECT?
   A. A lumbar puncture is contraindicated
   B. Infection is not likely as he does not have a fever
   C. Vaccination history is important information in this case
   D. Little risk of contagion from this clinical presentation
   E. A CT scan of the head is the initial diagnostic test
**Answers:**

1. D— hyperthermia is not related to pyrogenic cytokines but rather a failed thermoregulatory homeostasis. Pattern of fever in current medical practice is often not helpful. Most persons feel uncomfortable from chills and sweats when you rapidly bring down a fever. Fever from non-infectious causes (such as heat stroke) is more often associated with very high temperatures compared to infections. The preoptic area of the hypothalamus controls body temperature.

2. C—A one-month-old child with a fever (>100.4) is a medical emergency and a serious bacterial infection needs to be ruled out. A CBC to assess for signs of infection (i.e. leukocytosis/leucopenia/ left shift) is essential as is a blood culture to check for bacteremia. Urinary tract infections(UTI) commonly present in the first few months and a urinalysis and urine culture are essential. While a BUN/Creatinine may be helpful in assessing the hydration status of this child who has had decreased oral intake (po), it will not help with your investigation of possible infectious etiologies for the fever.

3. B—The cerebrospinal fluid cell count is consistent with meningitis. HSV, Group B Streptococcus, and E. coli are all very common pathogens causing meningitis in the newborn period, while S. aureus is not.

4. D—This is a classic presentation of young girl with a UTI. She has no respiratory symptoms so a chest x-ray is not warranted and blood chemistries are unlikely to help you sort out a bacterial infection. A lumbar puncture would be warranted in this child if she is ill-appearing. One could argue that all febrile children under 60 days old need an LP, but it would be especially true if she was toxic or ill-appearing. A urinalysis is likely to be the most helpful test.

5. C- Like college students, basic recruits are at risk for meningococcal infection. This is suggested by his fever (100.4 degrees F), toxic appearance, neck stiffness, new petechial rash. It would be helpful to know if and when he received a meningococcal vaccine. Lumbar puncture (LP) is the diagnostic test of choice for meningitis. This is a rapidly progressive severe illness, unless he has focal neurologic findings on your examination a young person does not have to get a CT scan before doing a LP. If you need to get a CT for neuro findings start meningitis treatment before the CT (it will affect your cultures from spinal fluid). Meningococcal close contacts need to receive antibiotic prophylaxis after exposure as it is a contagious condition.
References

Introduction to Clinical Reasoning:
HIV Infection
Amy Weintrob, MD

A 19 year old female presents to her primary care physician complaining of a sore throat for 3 days, inability to eat, fever, fatigue, body aches, and a rash. She is on summer break from college and has generally been well although she did present to the health department two weeks ago complaining of a vaginal discharge. She was diagnosed with gonorrhea and treated with Ceftriaxone. She notes that on that visit she had a syphilis test and an HIV test, both of which were negative.

Questions:
1. What is your differential diagnosis for her symptoms?
2. How would you proceed in working up her symptoms?
3. How do you interpret her negative HIV test?
4. How would your differential diagnosis change if the same symptoms were seen in a 40 year old with a 40 lb unintentional weight loss over a year and 2 recent episodes of pneumococcal pneumonia?

Objectives:
Following the lecture and the small group discussion sessions, the student should:
1. Understand how HIV is transmitted and what factors affect the transmission of HIV.
2. Understand the clinical manifestations of HIV infection from primary infection to late stage AIDS.
3. Understand which types of opportunistic infections people with different levels of immune function develop.
4. Understand what factors are used to determine when to initiate therapy for HIV infection.
5. Recognize when post exposure prophylaxis against HIV is needed.

Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus: 2009 Update by the HIV Medicine Association of the Infectious Diseases Society of America Clinical Infectious Diseases; 2009; 49: 651-681

Overview:

HIV infection can present in a myriad of ways with a number of complications. This section will review key definitions, pathogenesis, natural history, complications, and a rationale diagnostic and therapeutic approach to a patient with HIV infection. A number of key findings, heuristics (rules of thumb), and patterns (pattern recognition) will be illustrated through example cases and discussion.

Definitions:

HIV: Human immunodeficiency virus, a retrovirus (meaning the virus contains RNA which is then reversely transcribed into DNA) which can infect immune system cells and lead to decreased immune function.

Acquired Immune Deficiency Syndrome (AIDS): a syndrome characterized by an ineffective immune system, an opportunistic infection, or certain malignancies (associated with oncogenic viruses) caused by infection with HIV. Not everyone with HIV has AIDS!

CD4+ T cells or T helper cells: lymphocytes which express the surface protein CD4. CD4 cells bind antigens presented by antigen presenting cells and are then activated releasing cytokines and other substances which then stimulate the activity of macrophages, natural killer cells, cytotoxic T cells (CD8+ T cells), and B cells (which produce antibodies). HIV binds to the CD4 receptor in the presence of a chemokine co-receptor and can then enter the cell.

Viral load (HIV RNA PCR): The number of copies of HIV per specific volume of blood.

Primary HIV Infection or Acute Retroviral Syndrome or Acute HIV Infection: The period of time after HIV infection but before HIV antibody production that is characterized by massive viral replication and a flu-like symptomatic illness. Because HIV antibodies are absent during this time, HIV diagnosis has to be made by looking for the virus itself (usually by HIV RNA PCR or a 4th generation HIV test that detects the HIV p24 antigen along with antibodies).

Highly active antiretroviral therapy (HAART): a combination of at least 3 antiretroviral medications used to treat HIV infection. This is also referred to as Combination Antiretroviral Therapy (cART).

Immune reconstitution inflammatory syndrome (IRIS): paradoxical worsening of a condition or the appearance of a new condition after starting ART due to restored function of the immune system.
Epidemiology of HIV Infection:

Since the beginning of the HIV epidemic, more than 60 million people have contracted HIV and nearly 30 million have died of HIV-related causes. In 2012, more than 34 million people worldwide live with HIV/AIDS, with more than two-thirds living in developing countries. It is reported that an estimated 3.4 million of those infected are under the age of 15. In 2011, 2.5 million people were newly infected with HIV, with an estimated 1.7 million deaths from AIDS.

Despite increased knowledge about the transmission of HIV, the number of newly infected persons has remained stable in the United States (50,000 persons infected per year). In the U.S., 49% of transmitted cases are due to male-to-male sexual contact, 32% are due to heterosexual contact, 14% are due to intravenous drug use, and the remaining 5% are due to other or unknown risk factors. The highest rates of increased transmission are amongst young black gay and bisexual males.

HIV Virus and Life Cycle

HIV is an RNA virus. The nucleic acid is packaged together with reverse transcriptase, an enzyme which converts the RNA into DNA after it enters the host cell. The RNA and reverse transcriptase are enclosed in p24 capsule proteins. This p24 capsule is surrounded by an envelope studded by glycoproteins called gp41 and gp120.

The glycoproteins on the surface of the virus bind to the CD4 receptor located on the surface of certain host cells and in the presence of a chemokine co-receptor, the virus is able to penetrate the host cell. The nucleic acid is uncoated and the reverse transcriptase enzyme converts the RNA into DNA which is then able to enter the nucleus of the host cell. Once in the nucleus, it can integrate with the host DNA. If the host cell is latent (not actively replicating, such as with memory cells), the viral nucleic acid remains latent as well. If the cell replicates, the viral nucleic acid is transcribed then translated into proteins. Viral RNA is packaged along with the translated proteins. The assembled viral capsule then buds from the host cell surface and matures into a virion that can infect other cells. Antiretroviral medications only work on replicating viruses; they do not work on latently infected cells which are one reason they do not cure HIV infection.

Transmission of HIV

HIV can be transmitted through blood or plasma (such as from transfusions, intravenous needle sharing, or occupational needle sticks) or through bodily fluids such as semen, cervicovaginal fluid, breast milk, or cerebrospinal fluid. There are certain body fluids that do not transmit HIV including tears, saliva, urine, and stool.
The risk of transmission depends on the mode of transmission and the HIV stage of the transmitter. The table below lists estimates of the risk of transmission for certain modes.

<table>
<thead>
<tr>
<th>Mode of Transmission</th>
<th>Risk per act/exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive anal intercourse</td>
<td>0.8 – 3.2%</td>
</tr>
<tr>
<td>Receptive vaginal intercourse</td>
<td>0.05 – 0.15%</td>
</tr>
<tr>
<td>Insertive vaginal intercourse</td>
<td>0.03 – 0.09%</td>
</tr>
<tr>
<td>Risk with needle stick</td>
<td>0.3%</td>
</tr>
<tr>
<td>Occupational mucocutaneous exposure</td>
<td>0.09%</td>
</tr>
<tr>
<td>Maternal-Fetal</td>
<td>20 -30%</td>
</tr>
</tbody>
</table>

The risk of transmission is higher if the infected person has high plasma levels of HIV RNA as can be seen in patients with primary HIV infection or advanced AIDS.

After transmission, the virus infects dendritic cells in the lamina propria. The infected dendritic cells migrate to epithelial surfaces to sample antigens for presentation to T-cells. Within 48 hours of transmission, infected cells can be found in regional lymph nodes. Lymphocytes travel through these lymph nodes, become infected, and spread virus throughout the body.

Course of HIV Infection

After human infection, viral replication dramatically increases and the viral load (HIV RNA), or the amount of virus in the plasma, increases to well over a million copies of virus per milliliter of plasma. As viral replication increases, CD4+ T-lymphocytes (helper cells which release cytokines which activate other cells in the immune system) decrease. The plasma viral load peaks approximately 2 weeks after infection. Afterwards, the body is able to form a limited HIV-specific cytotoxic T-lymphocyte response which limits the increase in viral replication. The viral load decreases and the CD4 count increases. The immune system, however, is not able to completely clear the virus and the viral load decreases to what is termed the set point. The viral load (HIV RNA) set point is a balance between the virus’ ability to replicate and the body’s ability to keep viral replication in check. Some individuals have high viral load set points and some individuals have low viral load set points. Genetics (certain HLA types) play a role in determining the viral load set point. The set point is usually reached within 3 months of infection. Afterwards, the virus continues to replicate and CD4 cells gradually decrease until the host starts developing illnesses due to having a deficient immune system. The period of time
between set point and significant immunodeficiency is variable, ranging from 1 year to over 20 years with the use of antiretrovirals. The set point is one factor that determines how fast someone progresses to immunodeficiency (the higher the set point, the faster the progression).

The course of HIV infection described above is associated with different clinical manifestations of HIV. During the first 2 weeks after infection, when the virus is rapidly replicating and CD4 counts transiently decrease, the infected person may develop a flu-like syndrome called *Primary HIV Infection or Acute Seroconversion Illness or Acute Retroviral Syndrome*. The acute illness subsides as the HIV-specific immune response decreases the viral replication. Once the set point viral load is reached, the infected person is no longer symptomatic and enters a stage called *Asymptomatic HIV Infection*. When they start developing symptoms from HIV replication (such as wasting), this is called *Symptomatic HIV Infection*. With continued infection, they develop a deficient immune system and they are susceptible to opportunistic infections and cancers and this stage is called AIDS (acquired immune deficiency syndrome). Not all HIV-infected persons have AIDS--only those whose immune systems are deficient (as described more below).

**Primary HIV Infection (PHI)**

PHI is the period of time after acquisition of the virus that is characterized by massive levels of viral replication, decreases in the CD4 count, an expansive immune response, and a symptomatic illness. It usually occurs two weeks after transmission and self-resolves after 1 – 2 weeks. Below is a list of symptoms associated with PHI and their frequency:

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>% of PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&gt;80-90</td>
</tr>
<tr>
<td>Fatigue</td>
<td>80-90</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>50-70</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>20-70</td>
</tr>
<tr>
<td>Rash</td>
<td>50-60</td>
</tr>
<tr>
<td>Myalgias</td>
<td>50-60</td>
</tr>
<tr>
<td>Headache</td>
<td>50-60</td>
</tr>
<tr>
<td>Nausea</td>
<td>30-60</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>20</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
</tr>
</tbody>
</table>

30:5
PHI is also associated with physical exam and laboratory abnormalities. The following list demonstrates the most common signs associated with PHI and their frequencies:

<table>
<thead>
<tr>
<th>SIGN</th>
<th>% of PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>40-50</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40-50</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>40-50</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>20-30</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>20-30</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>10-30</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

The diagnosis of PHI is difficult to make for 3 reasons: 1) the symptoms associated with it are very non-specific, 2) the diagnosis requires specialized testing, and 3) since the symptoms self-resolve, some infected individuals do not seek medical attention for their symptoms. Diagnosis therefore requires a high index of suspicion. The screening test for HIV infection is an HIV ELISA which detects antibodies generated against HIV. Antibodies are not formed until 20 – 30 days post infection and since the symptoms of PHI start 14 days after infection, the HIV ELISA is negative during PHI. If the HIV ELISA is positive, it has to be confirmed with a positive Western blot (which detects antibodies to certain HIV antigens) before the test can be considered positive. Again, during PHI, the Western blot may not be positive as symptoms occur before antibody formation. Therefore, in order to evaluate for PHI, you cannot simply order a routine HIV screening antibody test, but rather you have to look for the virus itself. This is a key finding. In the past, a p24 antigen assay was done to evaluate for PHI. It is positive early during symptomatic PHI but it may become negative during the later end of PHI as antibodies start forming against the p24 protein and inhibit its detection. The diagnosis of PHI can be made by evaluating for the virus with HIV RNA PCR. The PCR is more sensitive than the p24 assay, it is positive earlier in disease, and stays positive longer. The HIV RNA PCR is usually what is relied upon in the right clinical setting to diagnose PHI. It should be ordered in conjunction with an HIV ELISA to rule out chronic HIV infection. A recently approved combination immunoassay that detects antibodies to HIV-1 and HIV-2 and detects the p24 antigen can also be used to diagnose acute HIV infection (a positive p24 antigen with negative HIV antibodies would indicate acute infection).
Despite the difficulty in diagnosing PHI, making the diagnosis is of great importance to both the infected person and to public health. Regarding the infected person, they will benefit from being referred for care early in infection before their immune system is deficient. Regarding public health, PHI is one of the most infectious stages of HIV infection. Therefore, to decrease the spread of new infections and potentially preserve immune function, diagnosis is critical.

**Answers to Questions 1-3:**

**Problem List:**

1. Fever  
2. Sore throat  
3. Rash  
4. History of gonorrhea (treated)

The differential diagnosis for a 19 year old with a sore throat, fatigue, fever, and rash with a recent STD should include: Primary HIV Infection, Viral mononucleosis, Group A streptococcal infection, disseminated gonorrhea, Rocky Mountain Spotted Fever, Influenza, Coxsackie virus, mycoplasma infection, secondary syphilis.

Viral mononucleosis can be caused by EBV or CMV and could present with her similar symptoms. It is very difficult to distinguish viral mononucleosis from Primary HIV Infection and in fact a useful heuristic (rule of thumb) for your practice is: **if you think mono, you should also think Primary HIV Infection!**

Group A streptococcus can cause a sore throat, fever, fatigue and even a rash. Often the infected person will have exposure to children or to someone recently diagnosed with strep pharyngitis. On exam, strep throat is more likely to be characterized by thick white exudates over the tonsils than PHI.

In disseminated gonorrhea, the rash would be characterized by a small cluster of pustules as opposed to the rash associated with PHI which is usually erythematous and maculopapular.

Rocky Mountain Spotted Fever can cause fever, rash, and fatigue although it usually does not cause sore throat. Syphilis does not usually cause sore throat either.

Other viral illnesses such as Influenza or Coxsackie (which causes hand-foot-mouth disease) could cause her symptoms. Since she’s on her summer break, winter viruses such as influenza may be less likely (although this may depend on whether there’s an outbreak of a novel influenza virus). On exam, Coxsackie is characterized by vesicles (blisters) in the mouth, feet and hands.

To further evaluate her symptoms, you would order an HIV ELISA (routine HIV test) to screen for underlying chronic HIV infection as well as an HIV RNA PCR to evaluate for PHI. You would also order a monospot test to evaluate for viral mononucleosis caused by Epstein Barr...
virus (EBV). If her throat demonstrated erythema or pustules, you could perform a throat culture (swab) for Group A streptococcus.

Her “HIV test” was negative because the Health Department ordered a routine screening HIV test (ELISA). Symptoms of PHI start before you develop antibodies to the virus so the ELISA will be negative during PHI. An important rule of thumb (heuristic)--a negative “HIV test” does not rule out primary HIV infection!

Case continued: The patient’s monospot test was negative; however, the HIV RNA PCR was positive (viral load = 3 million copies/ml). She was counseled regarding the HIV positive test and referred to an Infectious Disease specialist for follow up. She contacted her boyfriend and recommended that he be tested for HIV. He did so and was found to have a positive HIV ELISA and Western blot. The boyfriend had been in good health and had no recent illnesses or weight loss.

Question 5: What laboratory tests do you want to obtain on both patients? What counseling would you give the patients?

Question 6: Should they be started on antiretroviral agents? Should they be started on any other medications?

Asymptomatic HIV Infection

Asymptomatic HIV infection is the stage of infection after PHI but before the patient develops any symptoms from the virus itself or from destruction of the immune system. The length of untreated asymptomatic HIV infection is variable (<1 year - >20 years) and probably depends on both characteristics of the individual viral strain as well as characteristics of the infected individual and the status of their immune system. Some HLA types have been associated with slower disease progression and longer asymptomatic periods. A small proportion of HIV-infected individuals are long-term non-progressors, meaning that despite being infected for many years (often > 7-10 years), they do not progress to any illnesses or exhibit progressive immune system destruction, as is usually expected. Even rarer are elite controllers, individuals who are not on antiretroviral therapy but who have viral loads below our ability to detect them (despite detectable antibodies against HIV).

Just because HIV-infected individuals in this stage do not have symptoms, this does not mean that the virus is latent. Viral replication is ongoing and CD4 counts will slowly decline with time. HIV-infected subjects may lose subsets of CD4 cells that protect against certain infections even if the absolute number of CD4 cells remains within normal limits.

When seeing someone with asymptomatic HIV infection, it is an ideal time to start educating them about HIV, how it is transmitted, and how transmission can be prevented. It is important to discuss their social support network given the continued stigma surrounding the diagnosis of
HIV. Assessing their mental health is also important as depression is relatively common and can negatively impact quality of life and treatment adherence. Among a subset of patients with HIV, substance abuse is a significant problem and should be addressed. Given that HIV medications are expensive and must be taken for life, it is also important to discuss how they obtain (and pay for) their medications. Often, they should be referred to social work and psychiatry for further assessment of their social and mental health needs. They also need baseline laboratory assessments to evaluate the stage of their infection as well as for other sexually transmitted diseases, for conditions caused by HIV infection, and for conditions (e.g., latent infections such as tuberculosis or Herpes Zoster) which may worsen with HIV infection. To evaluate the stage of their infection, we order a CD4 count which is a measure of how many CD4+ T lymphocytes they have. \textit{CD4 counts < 200 predispose individuals to opportunistic infections; CD4 counts > 500 are within the normal range.} We also check a plasma viral load. \textit{Higher viral loads may predict faster disease progression and higher risk of transmission.} We also need a baseline viral load so we can assess the impact of the initiation of antiretroviral therapy. Since HIV can cause neutropenia, anemia, and thrombocytopenia, a complete blood count should be obtained. HIV can also cause a hepatitis and nephropathy so assessments of liver and renal function are indicated. \textit{Anyone with one sexually transmitted disease (i.e., HIV) should be screened for others so we check for gonorrhea, Chlamydia, and syphilis as well as for viral hepatitis (Hepatitis A, B, and C).} Several of the HIV medications can affect cholesterol levels; therefore, we evaluate a baseline fasting lipoprotein profile. Because some of the medications used can induce hemolysis in those who are G6PD deficient, we also check a G6PD level. Tuberculosis is more likely to reactivate in HIV infected persons so we place a PPD (purified protein derivative) skin test or order an interferon-gamma release factor assay to evaluate for latent TB. Toxoplasmosis is a latent infection which can reactivate with immune suppression so we check toxoplasma serologies (Toxoplasma IgG) to see if they have been infected with this in the past. We also order an HIV genotype which allows us to determine if their virus has any mutations that would make it resistant to any of the antiretroviral medications.

During the asymptomatic stage, it is also good to vaccinate HIV-infected persons against pneumococcus (the most common cause of pneumonia), influenza, and Hepatitis A and B, if they are not already immune.

\textbf{Answers to Question 5:} For these 2 patients with newly diagnosed HIV infection, they should have the following tests ordered: CD4 cell count, HIV RNA viral load, complete blood count, liver function tests, chemistries (including creatinine), RPR (test for syphilis), hepatitis A IgG, hepatitis B surface antigen/surface antibody/core antibody, hepatitis C IgG, fasting lipoprotein profile, G6PD, toxoplasma IgG, and an HIV genotype. They should also undergo testing for gonorrhea and Chlamydia and latent TB.

Patients should be counseled that HIV is a chronic infection that cannot currently be cured but can be well controlled with medications. They should be told that it is transmitted via infected blood or body fluids such as semen, cervicovaginal fluid, or breast milk. They should be warned...
against sharing needles or donating blood. They should be told that the only way to absolutely prevent the sexual transmission of HIV is to abstain from sexual activities but that condoms are very effective in preventing the spread provided that they are correctly used with every sexual encounter. Their mental health and social work needs should be evaluated.

**Case continued:** The boyfriend never returned to clinic for follow up after his first appointment. Three years later, he re-presented to clinic with weight loss, decreased appetite, fatigue, and diffuse lymphadenopathy.

**Question 7:** What is the differential diagnosis and how should this patient be managed?

**Symptomatic HIV Infection**

As mentioned previously, during the asymptomatic stage, viral replication is ongoing and CD4 cells gradually decline in number. Viral replication may increase and the patient develops symptoms due to the viral burden and immune dysfunction. The CD4 count may be between 200 – 400 cells/mm$^3$ and the viral load may be high (>100,000 copies/ml) or increased from their baseline. They may lose lymphocyte subsets that are only present in small numbers to begin with. *Typical symptoms include weight loss, loss of appetite, and fatigue. Patients may also begin to show signs of mild neurocognitive impairment or other signs of a worsening immune system such as a reactivation of herpes zoster (shingles).*

A complete history should be taken and physical exam performed in order to evaluate for other illnesses (related to HIV or not). Physical exam should focus on the oropharynx for the presence of thrush and other lesions, as well as the skin for rashes or lesions such as Kaposi’s sarcoma. Laboratory evaluation should include a CD4 count and an HIV viral load as well as other labs to evaluate for any conditions associated with HIV (complete blood count, liver function tests, creatinine, thyroid studies, adrenal studies, blood cultures if febrile, etc). The history and physical exam should guide what labs to order. The differential diagnosis will depend somewhat on the CD4 count.

**Answers to Question 7:** The differential diagnosis for his presentation includes symptomatic HIV infection, cancer, adrenal insufficiency, thyroid disease, and depression. Opportunistic infections are also possible. His diffuse lymphadenopathy makes thyroid disease, adrenal insufficiency, and depression less likely although he could have more than one diagnosis. He should have a complete history and physical followed by labs tailored to any abnormalities from the history or physical exam. A CD4 count should be done to evaluate his immune system and a viral load ordered. Further testing would be done based on his baseline labs and physical findings.

**Case continued:** Again, the boyfriend does not return for his follow up visit. One year later he presents with fever, cough, and shortness of breath for 3 weeks. His cough is mostly dry but he
cannot go up one flight of stairs without having to stop to catch his breath. He continues to lose weight.

**Question 8:** What is your differential diagnosis for his symptoms? How would you further evaluate him? What stage of HIV infection does he likely have?

**Acquired Immune Deficiency Syndrome (AIDS)**

In the vast majority of untreated HIV-infected individuals, over time HIV viral replication increases, CD4 counts decrease, and the individual becomes susceptible to opportunistic infections or malignancies. By definition, an HIV-infected person has AIDS when their CD4 count decreases to < 200 cells/mm³ (or CD4% < 14%) or they develop one or more of a defined list of opportunistic diseases (see list below):

- Candidiasis of bronchi, trachea, or lungs (not oral candidiasis)
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jiroveci pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

*Opportunistic infections are re-activated infections that were latent until immune surveillance waned* (examples include *Pneumocystis jiroveci* pneumonia [PCP], CMV retinitis, toxoplasmosis, or mycobacterium avium complex). Opportunistic malignancies are associated
with oncogenic viruses (examples include lymphoma associated with EBV, invasive cervical cancer associated with HPV, or Kaposi’s sarcoma associated with HHV-8).

The risk of certain opportunistic diseases depends on CD4 count. For example, PCP may occur at CD4 counts < 200 cells/mm³ whereas disseminated mycobacterium avium complex does not usually occur until CD4 counts fall below 50 cells/mm³.

Answers to Question 8:

Problem list:
1. Untreated HIV infection
2. Cough, shortness of breath (x 3 weeks)
3. Fever (x 3 weeks)

The differential diagnosis for 3 weeks of cough, fever, and shortness of breath in someone with known HIV infection includes PCP, tuberculosis, influenza or other respiratory viral pathogens (CMV does not usually cause pneumonia in HIV patients), community acquired pneumonia including atypical bacterial pneumonia, lymphoma, or lymphocytic interstitial pneumonia. Typical bacterial pneumonia (for example, pneumococcal pneumonia) usually starts more abruptly (acutely) and does not last as long as PCP, which characteristically has a more insidious onset. While the differential is broad in immunocompromised hosts, common diseases occur commonly and therefore work up should focus on the most likely diagnoses.

Laboratory evaluation should include a CD4 count, complete blood count, liver function tests, and an arterial blood gas (to assess oxygenation). If the patient is able to expectorate sputum, this should be sent for gram stain and culture. He should also have an induced sputum to evaluate for PCP. A PPD should be placed although these are often nonreactive in immunosuppressed individuals. Records of past PPD results should be obtained. A nasopharyngeal wash for respiratory viruses could be performed. A chest x-ray should be done. Further work up would depend on the results of these studies.

Assuming the diagnosis of PCP, this patient now has AIDS.

Answers to Question 4: The differential diagnosis of the original case presentation (fever, sore throat, inability to eat and a rash) drastically changes depending on the patient’s immune status. As noted before, if those symptoms occur in an otherwise healthy individual, the differential includes primary HIV infection, mononucleosis, Group A streptococcal infection, etc. If, however, the symptoms occur in someone with what seems like a more prolonged illness, one should think of chronic HIV infection with a superimposed opportunistic infection or malignancy. With a 40 lb weight loss over a year and 2 recent episodes of pneumonia, the person might have AIDS. The sore throat could be due to candidiasis (including esophageal disease), herpes, CMV esophagitis, or idiopathic ulcers associated with AIDS. The rash could be eosinophilic folliculitis (a pruritic rash associated with HIV infection).
Treatment of HIV Infection

The development of highly active antiretroviral therapy (HAART) has greatly improved the morbidity and mortality associated with HIV infection. The goal of ART is to achieve and maintain viral suppression (undetectable viral load lower than the limits of the assay). Exactly when to start ART has been an evolving topic since the introduction of antiretrovirals. Early on after the availability of medications in the mid 1990’s, a “hit ‘em early, hit ‘em hard” approach was taken but the side effects and toxicities of some of the medications were realized and a more conservative approach was adopted such that therapy was not initiated until CD4 counts decreased to 200 – 350. Recently, however, the medications available have become easier to tolerate with less side effects and toxicities and there is increasing evidence that viral replication is harmful even if the CD4 count is in the normal range. Therefore the guidelines have changed to initiate ART earlier in the course of HIV infection. DHHS guidelines are reviewed and updated several times a year based on emerging information on ART and can be viewed at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

Currently, therapy is recommended for all HIV-infected individuals to reduce the risk of disease progression. The strength of this recommendation, however, differs based on CD4 count. Therapy is also recommended to reduce the transmission of HIV.

Besides treatment of HIV infection, if a person’s CD4 count is low, we provide them with prophylaxis against opportunistic infections until their CD4 count increases and demonstrates some stability in this higher range. For CD4 counts < 50, we start prophylaxis against Mycobacterium Avium Complex (usually with azithromycin) and for CD4 counts < 100, we start toxoplasmosis prophylaxis (if toxoplasma IgG positive) with trimethoprim-sulfamethoxazole. For CD4 counts < 200, we start prophylaxis against PCP (usually with trimethoprim-sulfamethoxazole but other options include dapsone, inhaled pentamidine, or atovaquone).

Answers to Question 6: For the patient with Primary HIV Infection, treatment initiation is recommended. There are many potential benefits of starting HAART during PHI including: preserving immune function before further deterioration, lowering the set point viral load, decreasing transmission risk to others, preventing the emergence of random mutations that make the virus resistant to medications. When HIV-infected patients have opportunistic infections, the timing of HAART initiation is complicated by the potential to develop immune reconstitution inflammatory syndrome (IRIS). IRIS is the paradoxical worsening of a condition or the appearance of a new condition that occurs once the immune system is restored. For example, someone with HIV and PCP who is started on HAART may have a sudden increase in inflammation in the lungs due to HAART restoring part of the immune system. With increased lung infiltrates, oxygenation may temporarily worsen. Treatment of IRIS usually consists of continuing the treatment for both the opportunistic infection and HIV and sometimes steroids are used to temporarily decrease inflammation. Trials have shown benefits from starting HIV therapy early in the setting of certain opportunistic infections such as PCP but with others such
as cryptococcal meningitis, evidence points towards delaying HIV treatment until the opportunistic infection has received several weeks of treatment.

Treatment of the boyfriend is complicated by his non-compliance with his clinic visits. Once HAART is started, treatment is life-long and strict adherence is required in order to prevent resistance to the medications. Therefore, this patient needs frequent counseling regarding the importance of adherence with the medications and clinic visits.

Case continued: While at the clinic for follow up, the phlebotomist drawing the boyfriend’s labs sticks herself with the needle used to draw his blood. She immediately removes her glove and washes her hands.

Question 9: What is her risk of getting HIV from the needle stick? How should this occupational exposure be handled?

Occupational Exposure

The risk of HIV transmission from an occupational needle stick is approximately 0.3% (compared to Hepatitis C which is 3% and Hepatitis B which is 30%). The risk depends on whether the needle was solid or hollow bore (the latter has a higher risk of transmission), whether the needle had been in a blood vessel (higher risk), whether it had visible blood on it (higher risk), and whether it was a deep (higher risk) or superficial stick. It also depends on the stage of the infected person. There is a higher risk of transmission with PHI or AIDS than with asymptomatic disease. This risk of transmission from occupational mucocutaneous exposures is less than from needle sticks.

If an occupational exposure occurs, the area should be washed thoroughly and the person should present to occupational health immediately. If the HIV status of the source patient is unknown, he/she should undergo a rapid HIV test (which can be completed in 20 – 30 minutes). If negative, no further HIV testing is needed. If the source patient is HIV positive, the exposed person should have an HIV test (to evaluate for previous HIV infection) and be immediately started on post-exposure prophylaxis with antiretroviral therapy. Therapy is continued for 28 days and then the exposed person is periodically tested for HIV for 6 months after the exposure. Less than 10 healthcare workers in the U.S. have acquired HIV infection through occupational transmission.

Answers to Question 9: Her risk of acquiring HIV from the needle stick is approximately 0.3%. The source patient has AIDS and the needle was in his blood vessel both of which make this a high risk stick. She was correct in washing her hands. She should then report to occupational health for an HIV test and to initiate antiretroviral therapy. She should also be checked for viral hepatitis.
Case continued: The 19 year old who had PHI was immediately started on HAART. She was strongly adherent with the medication and followed up regularly in clinic. Two years later, she had an undetectable viral load and a CD4 count of 700. Upon presentation to the clinic for her next follow up visit, she informs her doctor that she is 3 months pregnant.

Question 10: What steps should be taken to reduce the risk of her child acquiring HIV from her?

Prophylaxis Against Maternal-Fetal Transmission

Prior to antiretroviral therapy, the risk of mother-to-child transmission was approximately 25 – 30%. With antiretroviral prophylaxis of the mother and the child, however, this rate has drastically decreased in the U.S. Mandatory perinatal HIV testing and the availability of HAART have nearly eliminated mother to child transmission in the U.S.

The highest risk of transmission is during delivery. The goal of therapy is to reduce the mother’s viral load to < 1000 copies/ml prior to delivery. If her viral load is higher, a C-section is usually performed to decrease the risk of transmission. The mother receives HAART during pregnancy and labor and after birth, and the infant is also given antiretroviral therapy. Breast feeding can transmit the virus so mothers in the developed world should be instructed not to breast feed.

Answers to Question 10: The mother’s current regimen should be reviewed to ensure that the medications are safe during pregnancy. She has an undetectable viral load, so if her medications are felt to be safe for the fetus, they should be continued. She should also be given intravenous antiretroviral therapy during delivery and her infant should receive antiretroviral therapy after birth. If her viral load is < 1000 c/ml at delivery, she could have a vaginal delivery. She should not breast feed.
Practice Questions (and answers): 

1. For which of the following HIV-infected patients is HAART indicated?
   a) 20yo pregnant female in her last trimester who is otherwise healthy
   b) 50yo male with disseminated Mycobacterium Avium Complex infection
   c) 32yo female with HIV-associated nephropathy
   d) Both B and C
   e) All of the above

2. Which of the following exposures is most likely to transmit HIV?
   a) Hollow bore needle stick from a needle that was used to draw blood on someone with AIDS
   b) Needle stick from a suture needle that was used to close the skin of someone with asymptomatic HIV infection
   c) Blood splash in the eyes from someone with symptomatic HIV infection
   d) Urine splash in the eyes from someone with AIDS
   e) Shaking hands with someone with Primary HIV Infection

3. A 45yo presents with fever, fatigue, maculopapular rash, and sore throat of 1 week duration. His physician orders a monospot and an HIV test, both of which are negative. Which of the following tests should you order to make the diagnosis of Primary HIV Infection?
   a) HIV Western blot
   b) CD4+ T cell count
   c) HIV RNA PCR
   d) CD8+ T cell count
   e) G6PD level

4. Which of the following patients is most at risk for developing Pneumocystis jiroveci pneumonia?
   a) 24yo started on HAART during Primary HIV Infection
   b) 19yo with HIV infection, most recent CD4 count of 150 cells/mm³, who has not regularly followed up with medical appointments and is on no medications
   c) 53yo with HIV infection, most recent CD4 count of 350 cells/mm³, who has not regularly followed up with medical appointments and is on no medications
   d) 42yo recently diagnosed with HIV infection, CD4 count of 100 cells/mm³ at diagnosis, who was started on HAART and Trimethoprim-Sulfamethoxazole daily 3 months ago
   e) 30yo with HIV infection and history of disseminated Mycobacterium Avium Complex who has been on HAART for 5 years with a most recent CD4 count of 525 cells/mm³
Answers

1. E – All of the above. Although the exact timing of when to start HAART is unclear, there are certain conditions where HAART initiation is indicated including pregnancy (to prevent transmission to the child), HIV-associated nephropathy, AIDS defining conditions (including disseminated Mycobacterium Avium Complex), and hepatitis B co-infection when the hepatitis requires therapy.

2. A – hollow bore needle which was in the blood vessel of the source patient with AIDS. All of these factors (hollow needle, in blood vessel, source patient with AIDS) make the exposure high risk. B is not correct because suture needles are solid which is associated with less transmission risk and the source patient had asymptomatic infection which is associated with less risk than someone with AIDS. C is not correct because mucocutaneous exposures (for example, eye splashes) are associated with less risk than needle sticks. D is not correct because urine does not transmit the virus. E is not correct because casual contact (hand shaking) does not transmit the virus. Although A is the correct answer, the exposed patients in A, B, and C would all receive post-exposure prophylaxis.

3. C - HIV RNA PCR. In Primary HIV Infection, antibodies to HIV have not formed yet therefore routine HIV tests (HIV ELISAs) will be negative. HIV Western blots will also be negative or indeterminate. To make the diagnosis, one needs to look for the virus itself. CD4 and CD8 counts are not diagnostic of Primary HIV Infection. An immunoassay that detects the p24 antigen in addition to HIV-1 and HIV-2 antibodies could also be used.

4. B – CD4 count of 150 on no medications. CD4 counts less than 200 cells/mm3 predispose to pneumonia with *Pneumocystis jiroveci*. Patients started on HAART during Primary HIV Infection usually have high CD4 counts. The patient in C is non-compliant with medical visits and is not on medications; however, the CD4 count is above 200 making them less at risk. D is not correct because although the CD4 count is low, the patient is on antibiotic prophylaxis against PCP making infection with this organism very unlikely. E is not correct because although the patient has a history of an AIDS defining condition, they have been on HAART for years and their CD4 count is now high.
ICR HIV Cases

The small group cases for this session will be the 3 patients that you will discuss as part of your Integrated Clinical Skills (ICS) experience on this topic.

Please complete the form on the next page for the patient that you wrote up during your ICS session. This form must be turned into your ICR preceptor at the beginning of the ICR small group session on this topic to receive credit. Please be prepared to give a 3 to 5 minute presentation of this patient for your ICR session.
Summary statement (1-3 sentences)

Prioritized problem list

1.
2.
3.
4.
5.
6.

Prioritized differential diagnosis (include at least 3 diagnostic options)

1.
2.
3.
4.
5.

Justification for leading diagnosis (history and physical exam findings and any ancillary data provided; write as a paragraph):

Plan (diagnostic work-up and/or therapeutic)

1.
2.
3.
4.
**HIV: Considerations in the Pediatric population…**

**CASE:** A previously healthy 4 month-old male arrives in the Emergency Department with respiratory distress. You enter the room and notice that the infant is working hard to breath, with noticeable nasal flaring and grunting noises. You quickly gather some history from the mother who states that the child had been doing well until two weeks ago when he developed a cough. His breathing has progressively worsened over the past six days. You ask the mother questions regarding his birth history and discover that she had poor prenatal care. She is unsure of any complications during the pregnancy but denies any difficulties with the labor and delivery. The baby born at term and the mother were discharged from the nursery after 48 hours. You ask about his well-baby exams and his vaccination status and the mother states that he is supposed to see the doctor next week.

On examination, he is febrile to 38.3°C with heart rate of 164/min, and a respiratory rate of 80/min and significant retractions. His oxygen saturation reads 84% on room air. Chest auscultation, however, revealed normal breath sounds without crackles, rhonchi, or wheeze. He has extensive white plaques on his tongue and buccal mucosa. Cervical, axillary, and inguinal lymph nodes are easily palpable. His spleen and liver are also generous in size. What could be the reason for this child’s respiratory distress?

Although the advent of Highly Active Antiretroviral Therapy (HAART) in the mid-1990s and the implementation of protocols designed to interrupt perinatal transmission of HIV have significantly reduced the number of young children with HIV/AIDS in the United States, cases of mother-to-child transmission still occur, particularly with mothers who have limited access to care and poor prenatal care. The U.S. Centers for Disease Control and Prevention (CDC) estimates that 100 to 200 infants with HIV infection are born each year in the United States.

When an individual develops acute HIV infection, his or her CD4+ T-lymphocytes are infected and significantly reduced in number. Although in most adults the CD4 count somewhat recovers and the viral load declines and hovers around a “set-point” after several months, about 20% of infected infants become “rapid progressors” in that their viral load continues to remain very high and their CD4 counts do not recover and progressively decline. Of these rapid progressors, all will die by age 4 without therapy, with a median age of death at 11 months. The other 80% of infected infants if they remain untreated will have mild symptoms and survive beyond 5 years of age. Because of the concern for rapid progression to AIDS, initiation of antiretroviral therapy is recommended in all infected infants regardless of clinical appearance, CD4 count, or viral load. Once an infant or young child is found to be HIV positive and placed on HAART, however, many of these individuals remain asymptomatic well into their adolescent years assuming they maintain good adherence to medical therapy.
Laboratory diagnosis of HIV infection in infants is based on detection of virus by polymerase chain reaction (PCR). Definitive exclusion of HIV is based on having at least 2 negative HIV DNA (or RNA) PCR tests, both of which were obtained at 1 month of age or older and one of which was obtained at 4 months of age or older. Serology does not have a role in diagnosis at this age because maternal antibody crosses the placenta; a positive serology in an infant may only reflect mother’s HIV status. However, in children 18 months and older, HIV antibody assays can be used to make the definitive diagnosis.

Presentations of HIV in the pediatric population, especially in the pre-HAART era, included unexplained fevers, generalized lymphadenopathy, hepatomegaly, splenomegaly, persistent oral candidiasis (thrush), failure to thrive, developmental delay, progressive neurologic disease, recurrent diarrhea, chronic parotitis, recurrent invasive bacterial infections, and various other opportunistic infections. Infants and young children were at greatest risk of developing one of these opportunistic infections when their CD4 count fell below 15% of total lymphocytes (equivalent to CD4 count of <750 in infants younger than 12 months, CD4 count <500 in children 1 to 5 years of age, and CD4 count <200 in those 6 years and older). One of the most common opportunistic infections in the United States in infants with perinatal acquisition of HIV is pneumonia from *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*). Classically it presents in infants with low-grade fever, cough, respiratory distress, and hypoxia. Chest radiographs typically show diffuse reticular interstitial shadowing, especially prominent in the hilar region. Because of the high incidence in this age group and the significant morbidity and mortality associated with *Pneumocystis* disease, all infants who are suspected of having HIV should receive prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) starting at 4-6 weeks of age. Other common infections in children with HIV/AIDS include *Streptococcus pneumoniae* bacteremia and pneumonia, chickenpox and shingles due to varicella-zoster virus, CMV, HSV, disseminated *Mycobacterium avium* complex (MAC), and *Candida* esophagitis.

One additional group at risk for HIV in the pediatric population is adolescents. According to the CDC, 39% of all new HIV infections in the United States in 2009 occurred in the 13-29 age group. It is therefore especially important to screen adolescents with high-risk sex practices for HIV because most infected adolescents are completely asymptomatic and without testing, they are unaware that they are infected.

Back to the case…

*You order a stat portable chest x-ray for your patient and have some baseline labs drawn. His radiograph demonstrates bilateral diffuse parenchymal infiltrates. His WBC returns at 13,000 with a hemoglobin of 12.6 g/dL, and platelets of 510K. His serum chemistry and liver function panel are normal. You notice however that he has very few lymphocytes (5%) on the differential*
of his CBC. You consider the possibilities for pneumonia or pneumonitis in an infant: bacterial causes such as pneumococcus or Haemophilus influenzae type B in the unvaccinated child, Chlamydia trachomatis transmitted from a mother with an unknown maternal infection history, complications following Bordetella infection, or even tuberculosis. You also consider in your differential viral causes such as severe infection from respiratory syncytial virus, influenza, or adenovirus. It is also possible that this may represent an aspiration pneumonia. Based on your findings of oral thrush, generalized lymphadenopathy, and hepatosplenomegaly, however, you being to wonder if you are dealing with an abnormal host. You have never seen a case of severe combined immunodeficiency but consider it in the light of the child’s absolute lymphopenia and oral thrush. HIV is also in the differential diagnosis as a cause for immunodeficiency in this patient. You remember that Pneumocystis pneumonia is a common presentation for infants with Severe Combined Immunodeficiency (SCID) or those infected with HIV. The patient is placed on a ventilator for impending respiratory failure. A rapid HIV antibody test on the patient comes back positive. A bronchoscopy is performed on the infant and the bronchoalveolar lavage fluid is positive for Pneumocystis by direct immunofluorescence. You begin targeted therapy with TMP/SMX and a three-drug HAART regimen and the patient slowly improves. The definitive diagnosis of HIV is confirmed in the patient with a positive HIV DNA PCR.
80 y.o. woman arrived at the Emergency Department (ED) at 0830 with a chief complaint of increasing weakness for 2 days and an episode of "a lot" of "coffee-ground" vomiting 2 hours before arrival at the hospital. She had a history of hypertension and described taking multiple medications although was not sure of all names but did state these included a daily aspirin and a beta-blocker for chronic atrial fibrillation. Gastric lavage in ED produces guaiac (hemoglobin) positive material that gradually converts to a clear effluent with multiple lavages. At the time of initial admission to the ED her blood pressure was recorded at 117/60 supine with a pulse of 110 and during the lavage decreases to 90/60. She was given a rapid infusion of one liter of normal saline and her blood pressure gradually returned to the slightly below initial admitting level. Her pulse after the fluid was noted to be 100 and irregular. Initial laboratory data obtained in the ED showed a (hematocrit) Hct 30 % (her baseline in the medical record from a hospital admission 2 months prior was 35%) and WBC 17,000. Her ECG showed atrial fibrillation with a variable rate of 100 -110 with some ST-T changes. The EKG from 2 months before showed a baseline rate of 90-95 with less prominent ST-T changes. A gastroenterology (GI) consultation was requested and per her history and by protocol she was scheduled for an immediate upper GI endoscopy. Orders for the transfer were written including an additional liter of saline to be infused during the procedure and she was sent directly to the endoscopy lab from the ED at 1330.

The UGI endoscopy revealed: “Stomach filled w/ clots. Active bleeding from duodenal ulcer encountered after clot removal and controlled w/ cauterization…” The GI staff that had supervised/staffed the endoscopy recommended that the patient be admitted to the ICU for observation, blood transfusion, an Hct checked every 6 hrs. X 3, and the IV administration of Proton. The GI fellow who actually performed the endoscopy wrote, without reviewing the orders written in the ED, the staff physician’s recommended orders along with basic admission medical orders in preparation for transfer to the ICU. His post-procedure and consult note did not contain a reconciled medication list. The post-endoscopy findings and recommended plan was discussed with ICU admitting medical resident following the procedure at 1500 while the patient was still in the endoscopy recovery area. As the patient had not left the recovery area by 1700, the day admitting resident who did not actually see the patient post procedure then signed off to oncoming night call ICU resident at 1730.

The ICU was full that evening. After discussion between the ICU and on-call floor Medical Resident, the patient, who appeared stable, still being held in the endoscopy recovery area, was transferred and admitted to 5 Center, a general medical unit on the Medicine service and arrived on the floor at approximately 1900. At 2100, the floor nurse found this patient to be in respiratory distress hypotensive, and bradycardic. A stat page was made for the on-call house officer.
The on-call Medical Resident arrived quickly at the bedside (this was the 1st time he had seen this patient – it was a busy night w/ 4 admissions and cross cover issues). After quickly reviewing the chart, he ordered a 1-liter bolus of normal saline, a 2-unit stat blood transfusion, and asked for the most recent Hct, which was 15%. The floor nurse had not seen or heard of this report – she had 8 patients that night. The Hct laboratory critical value result had been called to the post-procedure recovery unit, after the GI fellow’s orders had been recorded, and was sent to the ICU, in anticipation of the patient’s original transfer destination. The Blood Bank reported back to the nursing station on the 5 Center medicine floor that the patient had not had a type and cross-match order placed, and that no compatible blood was available for this patient. CPR was initiated, but the patient deteriorated rapidly and expired @ 2145.

Medical process errors calculated from chart review occur at an average rate of 10% of patient-system interactions. Some types of activity are higher risk, as an example, the incidence of inpatient medications errors has been calculated to be one error per patient per day. We know that are examples of complex adaptive systems and that healthcare delivery systems are not intrinsically safe or easy to work in. In A New, Evidenced-based Estimate of Patient Harms Associated with Hospital Care (James JT J Patient Safety 2013; 9: 122-127) the number of deaths per year due to preventable harm events calculated using the Global Trigger Tool is estimated to be 210,000 – 400,000. In addition serious harm is estimated to be 10 – 20 times more frequent than a death related outcome. It is only through the remarkable ability and the time consuming work of people to adapt and adjust that allows them to attempt to meet the multiple system goals: productivity, efficiency, effectiveness, timeliness and safety that they encounter every day. The occurrence of a medical error can be viewed as the symptom of a deeper abnormality, in much the same way that the complaint of shortness of breath can lead to a diagnosis of congestive heart failure. Just a physician learns to evaluate, interpret, and thoughtfully intervene in a most complex adaptive system, the human body, so can that approach be applied to the health care systems in which patients and providers interact.

To practice quality medicine, physicians must be aware of the causes (pathophysiology) of errors and understand the systems and component processes in which they develop in order to diminish their occurrence. In this session we will apply the principals of the clinical reasoning skills you have obtained during this course to the investigation of error events caused by system/process failures. As you will see, the point of these investigations is not simply to find where individuals went wrong but to understand why their assessments and actions appeared to make sense based on the circumstances at the time. We will treat the system as the patient and investigate the processes and people’s actions as symptoms and signs. Then through the use of a diagnostic method that you are now familiar with, ascertain the causes of the eventual error. It is important to realize that just as in human disease, it is routinely a combination of multiple contributing factors, each necessary, but not singularly sufficient, to stress a complex system to the point of failure.

To treat a patient you must take a complete and detailed history and supplement this information with other sources of data. Once this material has been collected, it is correlated, listed, and
analyzed. In incident analysis/investigation this sequence is known as the "root(s) causal analysis" and is the process used for identifying the basic or causal factors that underlie variation in performance. Introduction to Clinical Reasoning defines an accepted clinical reasoning approach to problem solving. It is also required to look, within a complex system, at the interactions among the various event components/factors recognizing that it these interactions and the rationale behind them that truly provide the insight into why events occur. This same clinical reasoning sequence, with slight modifications, is presented below and as applied to the understanding of the active and latent errors found within systems and processes that lead to the occurrence of a medical error. (Active Failures – Errors that occur at the level of the frontline operator, usually direct effect on the integrity of the defenses, and their results are felt almost immediately. These are the “sharp end” events at the human-system interface. Latent Conditions – The less apparent failures of organization or design processes where decisions regarding policies, procedures and resource allocations are made that contributed to the occurrence of errors.)

We will use two graphic tools to help define and analyze the event: the **flow diagram** and the **cause and effect ("fishbone") diagram.** These serve as a **problem list** and the subsequent **differential diagnosis** tool.

1. **Establish the database**
   a. Start with the question: Has this or something like this happened before?
   b. Inquire into the details of the event by engaging all those directly and indirectly involved in the event.
      i. Collect data concerning all areas (human factors, processes, systems) appropriate to the specific type of event. Just as the patient is one source, so are the medical record, family members, and other materials. In an incident evaluation sources include the patient, staff, records, established processes and procedures, and all contributors to the environment at the time of the event.

2. **Construct a sequence of events - "Course of the illness"**
   a. Develop a problem statement; i.e. Why did the outcome in question occur?
   b. This is best accomplished by the construction of **flow diagram** and is similar to the **concept map** approach described in the course introduction section on schemas.
      i. Establish through the flow diagram an accurate chronological sequence of the series of events preceding the event in question through the final known event. In this activity only the key events are recorded and leads to the next step.

3. **Identify key findings: Develop a "Problem List"**
   a. Review the **flow diagram**
      i. Identify the risk/failure points and their potential contributions to the event.
      ii. Use systems thinking - focus on processes that played a role at each point of the flow diagram.
      iii. Expect multiple causes with multiple interactions:
          - Proximate and contributing causes at point of direct care delivery (The "sharp end").
• Look for distant active or latent root causes imbedded in the system
• Anticipate multiple root causes with a resultant “cascade of events”.

4. **Formulate a differential diagnosis**
   Based on the data collected in Step 3, construct a cause and potential/observed effect(s) ("fishbone") diagram to identify the chains of causal links that lead to an understanding of the contributing factors to the event under study and its clinical outcome(s).

5. **Synthesize a diagnostic hypothesis: WHY DID THIS HAPPEN?**
   a. Based upon your cause and effect diagram, for each potential cause, perform an analysis of the underlying systems/processes through a series of "**what**" and "**how**" questions to determine the points of risk, until all aspects are reviewed and all contributing factors identified. **Remember the "why" questions are ultimately answered through an analysis of all the data obtained as described in the next step.**
   b. Apply the "Five Rules of Causation" (modified ESM NCPS Root Cause Analysis Tools 2002) to each of the identified contributing causes.
      i. Clearly show the cause and effect relationship
         Use specific and accurate descriptors for what occurred, rather than negative and vague words. (i.e. "The resident didn't follow-up." vs. "The resident was responsible for seven new admissions and cross cover on the floor. The critical laboratory data was reported to the floor as a part of a set of routine data and not identified as requiring immediate staff notification."
      ii. Identify the preceding cause(s), not the human error.
      iii. Identify the preceding cause(s) of process/procedure failures
      iv. In the case of an error of omission remember "Failure to act is only causal when there is a pre-existing requirement to act."

6. **Test the hypothesis: Therapeutic Approach**
   a. Development of a critical action plan through the determination of process/systems improvements that would reduce risk of event recurrence.
   b. Implement the action plan and monitor system for "near misses" (symptoms) and actual events (signs). If you know what you are trying to prevent and how many times its has happened before, **observing the system for unintended variation/outcomes** will provide the data necessary to determine if your analysis and interventions are successful.

**Cautions**
Just as there are common diagnostic reasoning failures that underlie most diagnostic failures, so too some of these exist in the evaluation of the medical incident. To reinforce and supplement materials you have seen before in this course.

**Stay Focused: Remember the underlying questions are what happened and why.** Do not short circuit the process by attributing causation before all the data is collected. Remember everything is potentially important. Just because you think it's obvious does not mean it is.

**Hindsight bias** is a common documented psychological phenomenon in which people exaggerate the predictability of an event after it has already happened. If you know the outcome it is easy to make up the cause.

**Premature Closure:** Just as most problems in medicine have at least 3-5 common causes so is it rare to find a single root cause as the basis for event. Failure to consider alternative causes (diagnoses) can lead to excluding serious latent errors that might be present.

**The "Bed of Procrustes":** Forcing an explanation (diagnosis) onto an implausible clinical scenario. It is well-documented human behavior that when faced with an unexpected and or "bad" event people tend to change the circumstances of the event or the role of the participants rather than change their basic beliefs about the systems or processes that facilitated the occurrence of the event.

**Medical Incident Analysis: Group Exercise**

In this exercise the course provides a single or sequence of events that can be directly observed by the students that trace the progression of a patient from their initial encounter through their course and outcome. Unlike the circumstance of evaluating and analyzing an event after it has occurred, as demonstrated by the case provided, you will not know the outcome(s) until the final scene is complete. In this circumstance will not be subject to “hindsight bias”. This is the very human tendency to pass judgment on the people and the events leading up to an accident when the outcome is known. Essentially this confers our perception of reality onto the events and individuals we are evaluating.

This educational activity is designed to duplicate the patient – physician clinical reasoning experience when one starts with the initial information, decisions are made, and the subsequent course of events and their outcomes are determined by the natural history of the underlying disease and the interventions related to the health care delivery system.

To make the most of this interactive case-based exercise you will call upon information provided in the communication series and concepts introduced in the Basic Introduction to Patient Safety. A number of the most salient topics are included here as definitions, comments, and principals.
An adverse outcome is an occurrence or condition associated with healthcare activities or health services when they cause unexpected harm to a patient during the provisions of such care or services. These may be because of acts of commission or omission.

An adverse event attributed to error is considered a “preventable adverse event.”

Preventability: Implies that methods or information for averting a given injury are known and that an adverse event results from failures to apply that knowledge.

An error is a failure of a planned action to be completed as intended (error of commission), a failure to take an appropriate action (error of omission), or the use of a wrong approach to achieve an aim (error of planning) that leads to an undesirable and unintended outcome.

The accumulation of errors results in accidents.

Due to the complex nature of systems, there is routinely no “single” or “root” cause for most accidents.

“We know that single causes are rare, but we don’t know how small events can become chained together so that they result in a disastrous outcome. In the absence of this understanding, people must wait until some crisis actually occurs before they can diagnose a problem, rather than be in a position to detect a potential problem before it emerges. To anticipate and forestall disasters is to understand regularities in the ways small events can combine to have disproportionately large effects.” Karl E. Weick

“Every system is perfectly designed to get the results it gets.”
Deming 1941

The observable result occurs at the “sharp end”, the point where the patient interacts with the system. The frontline interface relationship between the organization and its beneficiaries connects the organization’s core competencies with the needs of the individual patient.

Communication Points: “Handoffs” at the transition of care

Communication is the process by which information is transferred between individuals and within social structures and organizations.

Communication should be a two-way process of the exchange and progression of thoughts, opinions, or ideas towards a defined goal.

A successful oral case presentation provides the information that is important to allow for the listener to immediately apply clinical reasoning and to sustain this method of clinical thinking in the post presentation period.

- Allocation of sufficient time for communicating important information and for participant in the exchange to ask and respond to questions without interruptions is a major requirement.
The application of effective and accurate communication is essential for information to be directly transferred through an oral exchange and/or accessing the applicable medical records. This process must be accomplished to allow any healthcare provider as they become involved to respond in an appropriate and timely fashion to a patient’s specific needs.

A person’s thinking can be modified by the addition of a single piece of new relevant information, or by a diffuse increase in the relevance of a whole range of information.

Relevance is a term used to describe how pertinent, connected, or applicable something is to a given matter. A thing is relevant if it serves as a means to a given purpose.

Clinical relevance defines all data available about a specific patient.

Rhetorical Relevance: the logical framework in which communication trims away excess information to create the concise discourse necessary to make the required point(s). The rhetorical model breaks communication into four essential components: message, audience, purpose, and occasion.

- Rhetorical relevance defines that which is of interest to a particular audience for a specific patient related issue.
- Appropriate selection and level of detailed information required to maintain continuity of care and deal with evolving or new events.

Cascade of Contributing Causes

In reviewing a case keep in mind that the quality, safety, and value of care for any single patient or cohort of patients is a function of the sum of each interaction they have with the healthcare system.

You should consider error as a behavior and behavior, for our purposes, is described as the result of the interaction of a person and the environment. Look at what the people in this case are experiencing and look at the interactions that are occurring simultaneously. People do not act in isolation, the question to consider is why did a person act in a particular way at a particular moment, what influences were in play at the time, and what are the potential and actual effects of these influences on the individual’s final actions.

Examples for consideration of agents and interactions contributing to the failure/success of an intervention: a “provider” is anyone directly providing or supporting a patient care activity

a. Accident prone procedure
b. Provider/patient-family communication
c. Provider/Provider Communication
d. Provider/
e. Work space organization
f. Distractions
g. Fear
h. Frustration
i. “Handoffs” (transitions of care)
j. Human factors
k. Language
l. Noise
m. Provider hierarchy
n. Scheduling system
o. Stress
p. Teamwork
q. Technology
This is relatively simple flow chart of the sequence of events that occurred during the patient's transit through the hospital care delivery system on the day of her admission. Additional details can be added but for illustrative purposes this presentation contains the majority of the data set.

The benefit to this approach is that it gives the reviewer a base upon which to evaluate the various events and actions and determine their contribution to the eventual outcome. This flow is not intended to define cause and effect but begins the evaluation of the processes that lead to the observed sequence and the relationship of subsequent events. Without this essential "history", the clinical reasoning process necessary to arrive at a diagnosis of the event(s) cannot occur.
This represents an example of a reasonable cause-effect diagram for the evaluation of the example event. You may wish to include other points and you will this as the basis for additional data collection and then diagnostic hypothesis generation. Each one of these topic areas will have multiple components requiring evaluation.