Case 1

- A 46-year-old female with a history of rheumatoid arthritis presents to you with complaints of heavy menses and fatigue. In the past 18 months, her periods have become increasingly heavy for 3-5 days, requiring changing a maxi pad every 1-2 hours. She also complains of increasing pain and swelling of her hands and wrists for the past 6 weeks.

- On physical exam, there is mild tenderness of the MCP joints, pelvic examination is normal, and she appears pale. Laboratory studies are significant for WBC 5.2, Hgb 9.0 g/dL, platelets 290, MCV 76 fL, and RDW 14. Her erythrocyte sedimentation rate is 32 mm/hr. Ferritin is 42.
Which of the following would be the next best diagnostic test in elucidating the primary mechanism of her anemia?

- A. Serum c-reactive protein
- B. Serum iron
- C. Soluble transferrin receptor
- D. Bone marrow iron stores
- E. Reticulocyte count
Answer

C. Soluble transferrin receptor
Iron Deficiency Anemia

- Ferritin concentration is the gold standard test for diagnosis of IDA
  - Ferritin <15 ug/L is diagnostic of IDA, but IDA is likely when using a cut-off of <41 ug/L
  - Acute phase reactant
- Soluble serum transferrin receptor (sTfR) may be useful in diagnosis of IDA
  - Ratio of sTfR to ferritin
Iron Deficiency Anemia: treatment

- Ferrous sulfate tablets are the cheapest oral preparation
  - 66mg of elemental iron/tablet
  - Most cannot tolerate TID dosing

- IV iron therapy
  - Malabsorption
  - High iron requirements
  - Failure of oral iron
Clinical Pearl

- Low ferritin is diagnostic of iron deficiency, but is an acute phase reactant. Soluble serum transferrin receptor can be a helpful test in the diagnosis of IDA in patients with inflammatory conditions.
Case 2

A 73 year old Caucasian male reports for a routine physical examination. Past medical history is significant for hypertension and osteoarthritis, and he is taking metoprolol, naproxen, and a multivitamin. CBC shows a normal WBC and platelets, but hemoglobin 11.8 g/dL and MCV of 106. B12 level is normal.
Which one of the following is the most likely cause of the anemia?

- A. Anemia of chronic disease
- B. Folate deficiency
- C. Renal disease
- D. Alcohol use
- E. Thalassemia trait
Answer

- D. Alcohol use
Macrocytic Anemia

1. Medication use or alcohol excess?
   - NO
   - YES - Manage meds and alcohol

2. Homocysteine or B12 level abnormal?
   - YES
   - NO

3. MCV 97-110 fl
   - Check serum MMA
   - Consider MDS or other conditions

4. MCV >110
   - Consult hematology for probable MDS
Macrocytosis

- Medications
- Alcohol use
  - 80 grams EtOH/day = 1 bottle of wine
- Liver disease (from any cause)
- Reticulocytosis
- Hypothyroidism
- Copper deficiency
Clinical Pearl

- Causes of macrocytosis include medications that interfere with DNA metabolism, B12 and folate deficiency, reticulocytosis, myelodysplastic syndrome, liver disease, hypothyroidism, and alcohol use disorder.
Case 3

- A 65 year old male presents to establish medical care after recently moving to your area. He has not been seen by a physician in five years. He states that he takes no prescription medications and is generally healthy. He has never smoked. Exam is normal other than obesity. CBC shows a normal WBC and platelets, but hemoglobin is 18.8 g/dL. Repeat hemoglobin four weeks later is the same.
What would you recommend as the most appropriate next step in evaluation of his polycythemia?

- A. Erythropoietin levels
- B. Overnight oximetry
- C. CT abdomen
- D. Arterial blood gas
- E. Testosterone level
A. Erythropoietin levels
Erythrocytosis workup

- **Step 1:** repeat CBC in 1 month
- **Step 2:** determine if clonal vs. secondary
  - **Clonal**
    - Low epo level
    - JAK2 V617F mutation + in 97% of PV
Secondary Erythrocytosis

- Due to epo-response to hypoxia
  - High altitude, smoking, congenital heart disease, carbon monoxide toxicity
- Epo-producing tumors
- Drugs
  - Androgens and erythropoietin
Clinical Pearl

- The first step in evaluating persistent erythrocytosis is to determine if it is secondary or clonal via measurement of serum erythropoietin level.
A 71 year old female was found to have lymphocytosis on routine CBC. Further work-up with flow cytometry revealed stage 0 chronic lymphocytic leukemia. After consultation with the hematologist, she returns to your office and shares that she does not require CLL treatment at this time.
All of the following are true regarding this patient’s condition except?

- A. There is a higher risk of autoimmune cytopenias.
- B. All patients should be up to date with influenza, pneumococcal, and tetanus vaccines.
- C. There is a higher risk of non-hematological cancers compared to the general population.
- D. There is a higher risk of diffuse large B-cell lymphoma
- E. Prophylactic IVIG should be started due to the higher risk of infection.
E. Prophylactic IVIG should be started due to the higher risk of infection.
MBL and Early Stage CLL

- Higher risk of infections
  - Hypogammaglobulinenemia
    - IVIG prophylaxis if recurrent serious bacterial infections
  - Vaccines
    - Discuss live vaccines (zoster) with hematologist prior to administration
MBL and Early Stage CLL

- Secondary malignancies
  - Age appropriate cancer screening
  - Sun protection
  - Annual skin exam
Clinical Pearl

- Patients with MBL and CLL are at higher risk of infections and nonhematological cancers (particularly skin cancers) than the general population, even in the absence of CLL-directed therapy. Patients should have an annual skin examination, adhere to age-appropriate cancer screening, and be up to date with vaccines.
Case 5

- A 34 year old man is hospitalized after a motorcycle accident. He suffered multiple traumatic injuries, including splenic laceration requiring splenectomy and pneumothorax requiring chest tube placement. Today is post-op day 7, he is clinically improving, and hopes to be discharged today. Today’s CBC shows the following: WBC 10.5, hemoglobin is 12.5 g/dL, and platelets 832K. Platelet count was normal on the day of admission.
What is the next best step?

- A. Low dose aspirin and clopidogrel
- B. Peripheral blood smear
- C. Dismiss home
- D. Plateletpheresis
- E. Start heparin therapy
Answer

- C. Dismiss home
Reactive Thrombocytosis

■ Expected post-splenectomy
  - Peaks 1-3 weeks postop, normalizes within weeks
  - Generally not associated with thrombosis
    ▪ Consider ASA 81 mg
  - If extreme (>1500K), risk of hemorrhage

■ Other causes
  - Inflammatory conditions, infection, trauma, hemolysis, iron deficiency
Clonal Thrombocytosis

- Essential thrombocythemia (ET)
  - Increased risk of thrombosis if age >60 years and/or previous thrombosis
    - Platelet lowering agents + ASA
  - Increased risk of thrombosis if platelets >1 million
Clinical Pearl

Reactive thrombocytosis can be due to inflammatory conditions, infection, trauma, hyposplenism, hemolysis, and iron deficiency and does not cause an increased risk of thrombosis. No specific therapy is recommended.
A 63 year old Caucasian female reports for a routine physical examination. Past medical history is significant for hyperlipidemia, morbid obesity, diabetes type II, non-alcoholic steatohepatitis (NASH), hypertension, and osteoarthritis. Medication for the past three years have included aspirin, metoprolol, lisinopril, atorvastatin, metformin, and calcium/vitamin D. CBC shows a WBC 5.8, hemoglobin 12.8 g/dL and platelets 85K.
Which one of the following is the next best step for workup of the thrombocytopenia?

- A. Anti-PF4 antibody
- B. Prothrombin time
- C. Ultrasound of the abdomen
- D. HIV
- E. Peripheral blood smear
Answer

- E. Peripheral blood smear
Thrombocytopenia

- Can be due to inadequate production, sequestration, or peripheral destruction

- Step 1: is it real?
  - Peripheral smear
  - CBC in sodium citrate tube
Thrombocytopenia

- **Asymptomatic outpatients**
  - Immune thrombocytopenia (ITP), liver disease, HIV, myelodysplastic syndrome

- **Other causes**
  - Pregnancy, infection, medications, alcohol, malignancy, autoimmune d/o

- **Sick inpatients**
  - TTP/HUS, HIT, infection, medications
Clinical Pearl

- The first step in workup of thrombocytopenia is peripheral blood smear, both to rule out pseudothrombocytopenia and examine for other hematological abnormalities. Liver disease causes hypersplenism leading to splenic sequestration of platelets and is a relatively common cause of thrombocytopenia in the asymptomatic adult.
A 39-year-old African American healthy male presents to you for life insurance screening examination. He takes no medications and has no significant symptoms or past medical history. Physical exam is unremarkable. Laboratory studies show normal chemistries and lipids, but CBC is flagged as abnormal - WBC is 2.1 with a low absolute neutrophil count (ANC) of 1350. Hemoglobin and platelets are within normal range.
What is the most likely cause of the neutropenia?

- A. Lupus
- B. Lead exposure
- C. Benign Ethnic neutropenia
- D. Herbal medications
- E. Epstein-Barr virus
C. Benign Ethnic neutropenia
Neutropenia

- **Benign ethnic neutropenia**
  - African descent, Yemenites, West Indians, Arab Jordanians
  - ANC generally 1000-1500
  - Normal bone marrow reserve → no risk of infection
Neutropenia: Other Causes

- Congenital
- Infections
- Drugs
- Autoimmune
- Nutritional deficiency
- MDS
- Hematological malignancy
Benign Ethnic neutropenia is an inherited condition common in individuals of African descent. It causes mild neutropenia and does not carry an increased risk of infection.
Case 8

A 63 year old Caucasian female reports for a routine physical examination. Chemistry laboratories are significant for an elevated total protein, which leads to further testing. Serum protein electrophoresis shows an M-spike of 3.0 g/dL which is IgM kappa on immunofixation. Free light chains (FLC) are 232 kappa and 1.8 lambda with a FLC ratio of 128.9. CBC, creatinine, calcium, and bone survey are normal.
You give her the following diagnosis:

- A. Monoclonal gammopathy of undetermined significance
- B. Multiple myeloma
- C. AL amyloidosis
- D. Smoldering multiple myeloma
- E. Waldenstrom’s macroglobulenemia
B. Multiple myeloma
Multiple myeloma: diagnosis

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT†
    - Any one or more of the following biomarkers of malignancy:
      - Clonal bone marrow plasma cell percentage* ≥60%
      - Involved:uninvolved serum free light chain ratio§ ≥100
      - >1 focal lesions on MRI studies¶
TTP to symptomatic multiple myeloma from initial involved/uninvolved FLC ratio of $\geq 100$ versus a ratio of $<100$. Median TTP was 15 months in the FLC ratio $\geq 100$ group compared with 55 months in the FLC ratio $<100$ group ($P<0.0001$). At 24 months, 72% of patients with FLC ratio $\geq 100$ had progressed to MM versus 28% of patients with FLC ratio $<100$. 
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Low Risk (0 risk factors)</th>
<th>Intermediate Risk (1-2 risk factors)</th>
<th>High Risk (3 risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>M-spike &lt;1.5 g/l IgG type FLC ratio is normal</td>
<td>M-spike &gt;1.5 g/l and/or non-IgG type and/or Abnormal FLC ratio</td>
<td>M-spike &gt;1.5 g/l AND non-IgG type AND Abnormal FLC ratio</td>
</tr>
<tr>
<td><strong>Workup</strong></td>
<td>Bone marrow biopsy and skeletal survey not necessary</td>
<td>Refer to Heme for bone marrow biopsy</td>
<td>Refer to Heme for bone marrow biopsy</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>SPEP in 6 mos then q 2-3 years for life</td>
<td>SPEP in 6 mos then annually for life</td>
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</tr>
<tr>
<td><strong>Risk of progression at 20 years</strong></td>
<td>5%</td>
<td>21-37%</td>
<td>58%</td>
</tr>
</tbody>
</table>
Clinical Pearl

A serum involved to uninvolved FLC of >100 is now one of the diagnostic criteria for multiple myeloma based on the high risk of progression to end-organ damage.