Bookkeeping

• I have no conflicts of interest to disclose

• Final presentation available via email:
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• Who is in the audience?
Article selection

• Literature published Oct 2014-Sept 2015
  – ACP Journal Club
  – NEJM Journal Watch Hospital Medicine
  – The Hospitalist Newsmagazine (In the Literature)

• Criteria
  – Relevance to clinical hospital medicine
  – Impact on practice
  – Strength of study
Article analysis

• Case-based format
• Clinical question
• PICO
  – Patients
  – Intervention
  – Comparison
  – Outcome
• Results and recommendations
• ...and a few bonus “clinical shorts”
Case 1

- 76 yo M with COPD on home O2, HTN, BPH presents with acute onset of shortness of breath. No wheezing, no change in cough/sputum, no fevers. + right-sided chest discomfort, lightheadedness, leg swelling.
- Vitals: T 99.4, HR 111, BP 106/54, RR 22, SaO2 92% on 4L NC
- Notable exam findings: Appears to be in mild resp distress. Heart tachycardic, regular. Posterior lung fields clear. No rashes or tenderness to palpation in area of R side pain. Ext trace BLE edema with mild redness overlying R leg.
Case 1 continued

- Labs: WBC 9.6, Hct 41.5, Plt 362, creat 1.2, INR 1.1
- CXR: flattened hemidiaphragms, no acute process
- Chest CTA: pulmonary embolism
- Lower extremity Doppler US: RLE DVT

He is started on therapeutic dose LMWH and admitted to the hospital for further care. Because he has high clot burden, you think about consulting IR for placement of an IVC filter as a strategy to decrease risk of recurrent PE.
Clinical question

• Among hospitalized patients with severe acute pulmonary embolism, does the use of a retrievable inferior vena cava filter plus anticoagulation reduce the risk of symptomatic recurrent pulmonary embolism compared to anticoagulation alone?
Original Investigation

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism
A Randomized Clinical Trial

- **Patients** (17 French centers)
  - 18 years or older, hospitalized with acute, symptomatic PE associated with acute lower-limb deep vein or superficial vein thrombosis, plus 1 additional criteria for severity

- **Intervention** (n=200) & **Comparison** (n=199)
  - Randomized to retrievable IVC filter plus full-dose anticoagulation, with retrieval at 3 months, or anticoagulation alone

- **Outcome**
  - Fatal or non-fatal PE recurrence at 3 months

JAMA. 2015;313:1627.
Results

• Primary outcome: recurrent PE at 3 months
  – 6 patients (3.0%) in filter group and 3 patients (1.5%) in control group (RR with filter, 2.00, 95% CI, 0.51 to 7.89, p=0.50)

• Secondary and safety outcomes
  – No difference observed between the 2 treatment groups with regard to DVT, major bleeding, or death from any cause at 3 and 6 months
  – Filter complications included access site hematoma (5 patients), filter thrombosis (3 patients), retrieval failure (11 patients), cardiac arrest during insertion (1 patient)
Case 1 continued

• The patient is weaned back to his home oxygen levels and does well clinically. He is started on warfarin and outpatient follow-up is arranged.

➤ You are concerned that this patient had an “unprovoked” venous thromboembolism and may have an occult cancer. During your discharge handoff, should you recommend cancer screening to his PCP?
Clinical question

• In patients with a first, unprovoked venous thromboembolism, what is the efficacy of a screening strategy for occult cancer that includes comprehensive CT of the abdomen and pelvis, compared to a more limited screening strategy?
• Patients (9 Canadian centers)
  – 18 years or older with new diagnosis of first unprovoked symptomatic VTE (proximal lower extremity DVT, PE, or both)

• Intervention (n=423) & Comparison (n=431)
  – Randomized to limited screening (H&P, labs, CXR, sex-specific screening) plus comprehensive CT A/P, vs limited screening alone

• Outcome
  – Newly diagnosed cancer during the 1-year follow-up in patients with negative initial screening
Results

• 14 patients (3.2%) in the limited screening group and 19 patients (4.5%) in the limited plus CT group received a diagnosis of cancer in the interval between randomization and 1-year follow-up (p=0.28)

• Primary outcome
  – 4 of 14 (29%) occult cancers were missed by the limited screening strategy and 5 of 19 (26%) were missed by limited plus CT strategy (p=1.0)

• Secondary outcomes
  – No significant difference between groups in mean time to cancer diagnosis, rate of recurrent VTE, overall mortality, cancer-related mortality
Case 1 continued

• At discharge, you do not recommend an aggressive occult cancer screening for this patient.

• He does well for 4 months and unfortunately develops worsening obstructive urinary symptoms. He is seen by urology and has no improvement with medical therapy. He is scheduled for TURP.

➢ You are asked to see him for “medical clearance.”
CLINICAL SHORT: Should you add a β-blocker?

- What is the effect of perioperative β-blockade on patients undergoing non-cardiac surgery?
- Retrospective observational analysis of 326,489 patients undergoing surgery in VA hospitals from 2008-2013
- β-blocker use determined using pharmacy records
- 4-point cardiac risk score (renal failure, CAD, DM, surgery)
- Primary outcome: 30-day surgical mortality
- β-blockade lowered odds of mortality in patients with 3-4 risk factors, had no effect on patients with 1-2 risk factors, and had significantly higher odds of death in patients with no risk factors

Case 1 continued

• You do not start a perioperative β-blocker but do recommend that he hold his warfarin beginning 5 days before the procedure.

 Since he is only 4 months out from a major DVT/PE, you wonder if you should prescribe him enoxaparin bridging therapy?
Clinical question

- Should patients who are receiving warfarin for the secondary prevention of venous thromboembolism receive bridging therapy during warfarin interruption for invasive procedures?
Original Investigation

Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures

• **Patients** (Kaiser Permanente Colorado)
  – 18 years or older, receiving warfarin therapy for secondary prevention of VTE, undergoing an invasive diagnostic or surgical procedure

• **Intervention** (n=555) & **Comparison** (n=1257)
  – Use of bridging anticoagulation therapy vs no bridge therapy during warfarin interruption

• **Outcome**
  – Clinically relevant bleeding within 30 days of the procedure

JAMA Intern Med. 2015;175:1163.
Results

• Primary outcome: clinically relevant bleeding
  – 2.7% (15 events) in the bridge group vs 0.2% (2 events) in the non-bridge group (hazard ratio 17.2, 95% CI 3.9-75.1)

• Secondary outcomes:
  – No significant difference in recurrent VTE rates between bridge and non-bridge groups, even when analyzed by VTE risk category (9th edition of Antithrombotic Therapy guidelines)
CLINICAL SHORT! What if the patient was on warfarin for atrial fibrillation, and not VTE?

• In patients with atrial fibrillation/flutter, is heparin bridging needed during interruption of warfarin therapy before and after an invasive procedure?

• Randomized, double-blind, placebo-controlled trial of no bridge (n=950) vs dalteparin bridge therapy (n=934)

• Primary outcomes: 30-day arterial thromboembolism (stroke, TIA, systemic embolism) and major bleeding

• Incidence of arterial thromboembolism 0.4% in no bridge group and 0.3% in bridge group – met noninferiority

• Incidence of major bleeding lower in the no bridge group (RR 0.41, 95% CI 0.20 to 0.78, p=0.005)
Conclusion of case 1

- You do not prescribe bridging anticoagulation and the procedure and post-operative course are without complications.
Recap: what did we learn from case 1?

• DO NOT use retrievable IVC filters in patients with acute symptomatic PE who have high risk of recurrence but can be treated with anticoagulation
• DO NOT routinely perform CT abdomen/pelvis to screen for occult cancer in patients with a first unprovoked venous thromboembolism
• DO consider perioperative β-blockade in high-risk patients undergoing non-cardiac surgery. DO NOT use in patients with no cardiac risk factors.
• DO NOT automatically use bridge therapy for patients on chronic warfarin therapy (for VTE or atrial fibrillation) who require temporary interruption
Case 2

• 85 yo F with HTN, dementia, osteoporosis, hypothyroidism, stage 3 CKD presents with confusion from baseline and cough. She lives at home with her daughter and ambulates with a walker. No recent hospitalizations.

• She is afebrile, BP 140/74, HR 92, RR 20, SaO2 93% on 2L NC. Exam is notable for confusion and crackles at her R lung base. CXR reveals RLL infiltrate.

She is admitted to your service for treatment of community-acquired pneumonia
CLINICAL SHORT! What are safe and effective options for empiric antibiotic treatment for CAP?

- In patients with clinically suspected CAP admitted to non-ICU wards, what are the outcomes among different strategies of empiric treatment regimens?
- Non-inferiority trial with a cluster-randomized, crossover design
- 7 hospitals in the Netherlands
- Beta-lactam monotherapy (n=656), beta-lactam plus macrolide (n=739), or fluoroquinolone monotherapy (n=888)
- Primary outcome: 90-day mortality
- Empiric treatment with beta-lactam monotherapy was non-inferior to beta-lactam plus macrolide and fluoroquinolone monotherapy
- No clinically relevant differences in LOS or reported complications

NEJM. 2015;372:1312.
As you are acutely aware of your hospital’s efforts to reduce excess costs and length of stay, you decide to continue ceftriaxone monotherapy.

While entering your admission orders, you ponder other therapies that might favorably impact hospitalized patients with CAP. Might she benefit from steroids?
Clinical question

• For hospitalized adults with community-acquired pneumonia, what is the effect of adjunctive corticosteroid therapy on morbidity, mortality and duration of hospitalization?
• **Patients**
  – 13 trials of systemic corticosteroids in hospitalized adults with CAP

• **Intervention & Comparison**
  – Randomized to corticosteroid treatment (dexamethasone, prednisone, prednisolone, methylprednisolone, or hydrocortisone) or placebo

• **Outcomes**
  – All-cause mortality, need for mechanical ventilation, escalation to ICU, risk for ARDS, duration of hospitalization, time to clinical stability, adverse events
Results - Mortality

Severe pneumonia:
6 studies, n=388 patients
RR 0.39 (CI 0.20 to 0.77)

Less severe pneumonia:
6 studies, n=1586 patients
RR 1.00 (CI 0.79 to 1.26)
Results continued

• 5 studies (1060 patients) found a reduction in the need for mechanical ventilation in patients who received steroids (RR 0.45, CI 0.26 to 0.79)
• 3 studies (950 patients) found non-significant reduction in ICU admission (RR 0.69, CI 0.46 to 1.03)
• 4 studies (945 patients) found reduction in risk for ARDS (RR 0.24, CI 0.10 to 0.56)
• Steroid use decreased time to clinical stability by 1.22 days and duration of hospitalization by 1.0 days
• Steroid use increased the incidence of hyperglycemia requiring treatment but no effect on GI hemorrhage, severe neuropsychiatric complications, or rehospitalization
Case 2 continued

• Despite your evidence-based interventions of antibiotics and steroids, the patient becomes more hypoxic. She has a “do not intubate” order but her family agrees with ICU transfer due to hypoxemia.

➢ Is there a method of treating her hypoxia that might best prevent the need for intubation, while maximizing her comfort?
CLINICAL SHORT! Is high-flow oxygen through nasal cannula effective in hypoxemia?

• In patients with nonhypercapneic acute hypoxemic respiratory failure, what is the effect of high-flow oxygen on intubation rate, compared to standard oxygen through face mask or noninvasive positive pressure ventilation?

• Multicenter, open-label, randomized trial of 310 patients in 23 ICUs in France and Belgium

• Primary outcome: proportion of patients intubated at day 28

• Intubation rate was 38% in high-flow oxygen group, 47% in face mask group, 50% in NIPPV group (p=0.18 all comparisons)

• There was a significant difference in favor of high-flow oxygen on 90-day mortality; also increased comfort, decreased dyspnea, decreased respiratory rate

NEJM. 2015;372:2185.
Case 2 continued

• Fortunately, her respiratory status improves and she is transferred back to the floor.
• Two days later, she develops diarrhea and is diagnosed with *C. difficile* infection.

Aside from minimizing use of antibiotics, what can be done to decrease her risk of recurrent *C. difficile* infection?
Clinical questions

• Is proton pump inhibitor (PPI) use associated with a risk of *C. difficile* infection (CDI) recurrence?

• What proportion of patients who develop CDI are taking a PPI for a non-evidence-based indication, and are those patients candidates for PPI discontinuation to decrease risk of recurrence?
Continuous Proton Pump Inhibitor Therapy and the Associated Risk of Recurrent *Clostridium difficile* Infection

- **Patients** (2 hospitals in Montreal, Canada)
  - 754 patients who developed an initial episode of healthcare-associated *C. difficile* infection (CDI)
- **Intervention & Comparison**
  - Continuous PPI use vs no PPI use
- **Outcome**
  - Recurrence of CDI within 15 to 90 days of the initial episode

*JAMA Intern Med. 2015;175:784.*
Results

- 458/754 patients (60.7%) were taking PPI at initial CDI diagnosis
  - 3 patients had PPI discontinued
- 193/754 patients (25.6%) had documented CDI recurrences at 90 days
- PPI users more likely to experience a CDI recurrence (28.8% vs 20.6% compared to nonusers, p=0.007) and to die within 15-90 days of initial episode (10.3% vs 4.7%, p=0.007)
- Factors independently associated with risk of recurrence: age >75 years, continuous PPI use (HR 1.4, 95% CI 1.1 to 2.0), length of stay, vancomycin treatment of initial episode
- 52.9% of PPI users had no indication for PPI use
Conclusion of case 2

- She was treated with a course of flagyl and her PPI (for which there was no clear indication) was discontinued. She improved from both a pneumonia and diarrhea standpoint and was transferred to SNF at discharge.
Recap: what did we learn from case 2?

• DO consider use of beta-lactam monotherapy when treating community-acquired pneumonia in adults admitted to non-ICU wards

• DO consider administration of systemic corticosteroids to adults hospitalized with community-acquired pneumonia

• DO consider use of high-flow oxygen via nasal cannula in patients with nonhypercapneic acute hypoxemic respiratory failure

• STOP unnecessary proton pump inhibitors in patients diagnosed with C. difficile infection
Case 3

• 66 yo M with HTN, atrial fibrillation on warfarin, HLD, DM on insulin, OA who is admitted to the hospital with NSTEMI. He undergoes cardiac catheterization and PCI to mid-RCA with DES. Cardiology recommends 1 year of dual antiplatelet therapy with aspirin and clopidogrel.

➢ What do you do about his warfarin?
Clinical question

• Among older patients with myocardial infarction and atrial fibrillation undergoing PCI, what is the safety and effectiveness of triple therapy (warfarin, aspirin, clopidogrel) compared to dual antiplatelet therapy?
Use and Outcomes of Triple Therapy Among Older Patients With Acute Myocardial Infarction and Atrial Fibrillation

- **Patients** (n=4959 at 400 US sites)
  - Medicare patients 65 years and older with acute MI, history of atrial fibrillation or flutter, and underwent in-hospital PCI with stent placement

- **Intervention & Comparison**
  - Triple therapy (n=1370) vs dual antiplatelet therapy (n=3589)

- **Outcomes**
  - 2-year major adverse cardiac events (death, readmission for MI, stroke); bleeding readmissions

Results

• No difference between triple therapy group vs DAPT group with regard to 2-year post-discharge MACE:
  – 32.6% vs 32.7% (p=0.99)

• Adjusted hazard ratios with triple therapy:
  – All-cause mortality: HR 0.98, 95% CI 0.83 to 1.16, p=0.82
  – MI readmission: HR 1.03, 95% CI 0.79 to 1.33, p=0.83
  – Stroke readmission: HR 0.85, 95% CI 0.58 to 1.23, p=0.38
  – Ischemic stroke: HR 0.66, 95% CI 0.41 to 1.06, p=0.09
Results: Bleeding outcomes

Triple therapy associated with greater risk of bleeding requiring hospitalization and greater risk of intracranial hemorrhage

Case 3 continued

• The patient is discharged on aspirin and clopidogrel but not warfarin. However, he continues to take ibuprofen 2-3x per day for his severe knee pain related to OA.

➤ You question the risk of NSAID use in patients with history of MI – how does this affect bleeding and cardiovascular outcomes?
Clinical question

• What is the association of the concomitant use of NSAIDs with risk of bleeding and cardiovascular events among patients receiving antithrombotic treatment after myocardial infarction?
Patients (n=61971)
- 30 years or older admitted to hospitals in Denmark from 2002 to 2011 with first-time MI

Intervention & Comparison
- Using prescription claims, patients were classified into groups based on different combinations of aspirin, clopidogrel, vitamin K antagonists, and NSAIDs (including COX-2 inhibitors and non-selective NSAIDs)

Outcomes
- Risk of bleeding (requiring hospitalization); composite endpoint of cardiovascular death, non-fatal MI, stroke
Results

• Incidence rates of bleeding (events per 100 person-years) were 4.2 with concomitant NSAID treatment and 2.2 with no NSAID treatment (HR 2.02, 95% CI 1.81-2.26)

• Incidence rates of cardiovascular events were 11.2 with NSAID treatment and 8.3 with no NSAID treatment (HR 1.40, 95% CI 1.30 to 1.49)

• Increased risk of bleeding and cardiovascular events was demonstrated with concomitant use of NSAIDs, regardless of type of antithrombotic treatment, type of NSAID, or duration of use
Conclusion of case 3

- You recommend discontinuation of ibuprofen and treat his knee pain with acetaminophen, physical therapy, and topical treatments. He otherwise has an uneventful post-MI course.
Recap: what did we learn from case 3?

• DO NOT discharge older patients with atrial fibrillation/flutter on triple therapy following acute MI and coronary stenting

• USE CAUTION when prescribing (or endorsing OTC use of) NSAIDs in patients receiving antithrombotic therapy following myocardial infarction
References

References continued


• McDonald EG, Milligan J, Frenette C, Lee TC. Continuous proton pump inhibitor therapy and the associated risk of recurrent Clostridium difficile infection. JAMA Intern Med. 2015;175(5):784-791.


Questions

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