Update in Hospital Medicine 2008

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Case Presentation

A 72 year old woman with diabetes and hypertension presents with fever, chills, and a productive cough. She is diagnosed with community-acquired pneumonia (PSI of 85, class III) and admitted to the hospital. She is started on guideline-recommended antibiotics.

You get to the bottom of the admission order set and you can choose between UFH and LMWH for DVT prophylaxis. You wonder . . .

How does LMWH compare with UFH for VTE prophylaxis?

A. LMWH is associated with a lower risk of thrombocytopenia than UFH.
B. LMWH leads to a higher rate of bleeding when compared with UFH.
C. LMWH reduces the risk of DVT when compared with UFH.
D. Heparin? She don’t need no heparin. Squeezers, just squeezers, squeezing, squeezing, squeezing all day long . . .
VTE prophylaxis in medical patients

Question: Which agent most effectively prevents VTE in hospitalized medical patients?

Design: Meta-analysis, 36 prospective RCTs; 48,000 patients


Results

<table>
<thead>
<tr>
<th>UFH v. Control</th>
<th>LMWH v. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased VTE</td>
<td>Decreased VTE</td>
</tr>
<tr>
<td>No change in mortality</td>
<td>No change in mortality</td>
</tr>
<tr>
<td>Increase in bleeding</td>
<td>Increase in bleeding</td>
</tr>
<tr>
<td>TID dosing greater VTE reduction than BID</td>
<td>No difference in thrombocytopenia</td>
</tr>
</tbody>
</table>


Results: LMWH vs UFH

Compared w/ UFH, LMWH associated with...

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Reduced risk of DVT</td>
</tr>
<tr>
<td>Reduced risk injection site hematoma</td>
</tr>
<tr>
<td>No diff in risk of PE</td>
</tr>
<tr>
<td>No diff in total bleeds</td>
</tr>
<tr>
<td>No diff in mortality</td>
</tr>
<tr>
<td>No diff in thrombocytopenia</td>
</tr>
</tbody>
</table>


VTE prophylaxis in medical patients

Question: Which agent most effectively prevents VTE in hospitalized medical patients?

Design: Meta-analysis, 36 prospective RCTs; 48,000 pts

Conclusion: Both UFH & LMWH reduce DVT & PE in hospitalized medical pts. Neither affects mortality. LMWH, compared to all doses of UFH, was assoc w/ reduced risk of DVT; assoc w/ similar risk of PE. No difference in thrombocytopenia

Comments: LMWH probably better (enoxaparin 40mg SC daily)
Cost-effective vs. local pattern
If UFH, use TID dosing (5000 Units SC tid)

**How does LMWH compare with UFH for VTE prophylaxis?**

A. LMWH is associated with a lower risk of thrombocytopenia than UFH.
B. LMWH leads to a higher rate of bleeding when compared with UFH.
C. LMWH reduces the risk of DVT when compared with UFH.
D. Heparin? She don’t need no heparin. Squeezers, just squeezers, squeezing, squeezing, squeezing all day long . . .

**Case Continued**

She does well and has an uncomplicated hospitalization. On hospital day 3 you are preparing her discharge. As you are filling out her discharge prescription you pause to consider her antibiotic course for her pneumonia . . .

**What is the appropriate duration of treatment for her CAP?**

A. Treat her for a total of 2 weeks.
B. Wait, she only got 3 days of IV therapy. She needs to stay in the hospital to get 7 days of IV antibiotics.
C. Treat her for a total of 10 days
D. Treat her for a total of 7 days.  
E. Who cares. She probably won’t take it anyway. I hate my job.

**Duration of therapy in CAP**

A pie chart showing the percentage of patients treated for different durations of CAP: 49% treated for 2 weeks, 42% for 10 days, and 4% for 7 days.
### Duration of antibiotic therapy in CAP

**Question:** In pts with CAP, what is the appropriate duration of antibiotic therapy?

**Design:** Meta-analysis of 15 RCTs, 2796 pts with mild to moderate CAP

- Short (≤7d) regimen v. extended course
- Excluded trials w/ bronchitis, COPD, HCAP

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Risk of clinical failure: short v. extended course</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antibiotics</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>0.89 (0.78-1.02)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>0.88 (0.71-1.09)</td>
</tr>
<tr>
<td>β-lactams</td>
<td>0.92 (0.63-1.36)</td>
</tr>
</tbody>
</table>

**Conclusion:** Extended course therapy does not improve clinical outcomes in mild to mod CAP

**Comments:** Elderly patients were under-represented.

Some antibiotics (e.g. doxycycline) not evaluated.

Shorter courses probably effective (7 days).

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**What is the appropriate duration of treatment for her CAP?**

- A. Treat her for a total of 2 weeks.
- B. Wait, she only got 3 days of IV therapy. She needs to stay in the hospital to get 7 days of IV antibiotics.
- C. Treat her for a total of 10 days
- D. Treat her for a total of 7 days.
- E. Who cares. She probably won’t take it anyway. I hate my job.
**Short Take: Pneumococcal Vaccine**

- Prospective study, 3415 pts, 6 hospitals
- Patients hospitalized with CAP w/prior pneumococcal vaccination had 40% lower adjusted rate of ICU admission compared to those not previously vaccinated.


**Case Continued**

As you go to discharge her, the nurse says, "Oh, yeah, I forgot to tell you – she’s had like 6 watery bowel movements today and now she has a fever and pretty bad abdominal pain. Do you think she can go home?"

The patient is, in fact, febrile and tachycardic with severe abdominal pain. You check labs and her WBC is 28,000 x10^3/mm3. You suspect severe *Clostridium difficile* infection.

**What is the best therapy if this is severe *C. difficile*-associated diarrhea (CDAD)?**

1. Metronidazole (Flagyl®) 250mg PO q6h
2. Vancomycin 125mg PO q6h
3. Metronidazole (Flagyl®) 250mg IV q6h

**Treatment of *C. difficile***

**Questions:** What is the most effective treatment for CDAD? Does it depend on disease severity?

**Design:** Rand, dbl-blind, placebo trial 150 pts w/ *C. difficil*; 81 mild, 69 severe; Metronidazole PO v vanco PO x10d

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Vanco PO</th>
<th>Metro. PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cured</td>
<td>97%</td>
<td>84%*</td>
</tr>
<tr>
<td>Mild cured</td>
<td>98%</td>
<td>90%**</td>
</tr>
<tr>
<td>Severe cured</td>
<td>97%</td>
<td>76%*</td>
</tr>
</tbody>
</table>

* p < 0.05  ** p > 0.05

Severe = ICU, colitis, age>60, fever, wbc>15, alb<2.5

No difference in adverse events or relapse rates

**Treatment of C. difficile**

Question: What is the most effective tx for CDAD? Does it depend on disease severity?

Design: Rand, dbl-blnd, plac trial 150 pts w/ C. diff; Metronidazole PO v vanco PO x 10d

Results: Vanco = metronidazole for mild disease, Vanco superior for severe CDAD

Conclusion: Probably use vanco for severe CDAD

Comment: But, not for mild – cost difference, $6.60/pill vs. $0.11/pill


**Short Take: Probiotics**

- Prospective RCT of 135 patients compared probiotics (Lactobacillus) to placebo and showed a reduction in both 1) antibiotic-associated diarrhea and 2) C. difficile-associated diarrhea (CDAD)

- *Lactobacillus* in Ensure® for everyone?

Hickson M. BMJ. 2007;335:80.
Summary

- **Definitely**
  1) Prescribe *either* LMWH or UFH tid for VTE prophylaxis in medical patients
  2) Treat severe CDAD with vancomycin PO
  3) Give pneumovax to patients hospitalized with CAP

- **Consider**
  1) Giving antibiotics for 7 days or less for mild to moderate CAP
  2) Using LMWH instead of UFH for VTE prophylaxis

Case Presentation

A frail 89 yo woman (45kg) presents with chest pain and shortness of breath. Her vital signs and exam are unremarkable. Her EKG shows lateral ST-depressions and her troponin is 4.5mg/dL. She receives aspirin, metoprolol, and nitroglycerin. You contemplate the use of enoxaparin for her non-ST-elevation MI (NSTEMI) . . .

Which of the following is correct about use of enoxaparin in her NSTEMI?

A. She’s got a real MI, you should probably give her a little extra (50mg/kg BID).
B. She is pretty frail, probably best to underdose her a bit (40mg/kg BID).
C. Best to give her the right dose.
D. Enoxaparin? Don’t mess around – this 89yo needs a cath . . . NOW!

Enoxaparin Dosing Risk in NSTEMI

Question: In pts with NSTEMI, what is the relationship between enoxaparin dosing and outcomes?

Design: Observational study, from CRUSADE initiative, 10,687 pts, 332 hospitals

- Excess dose: >10 mg/d above recommended dose
- Under dose: >10 mg/d below recommended dose
- Rate of associated bleed or death
- Recommended dose for CKD was 1mg/kg daily

**Results: Enoxaparin Dosing in NSTEMI**

<table>
<thead>
<tr>
<th></th>
<th>Excess Dose</th>
<th>Recommend Dose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>14.2%</td>
<td>7.3%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>5.6%</td>
<td>2.4%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

- 18.7% received excess dose (58% of patients w/ CrCl <30)
- 29.2% received under dose


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**Case Presentation**

You prescribe the appropriate dose of enoxaparin and she has no bleeding complications. At cardiac catheterization, there are multiple 60% lesions but none that require intervention and she is discharged on appropriate medical therapy.

Eighteen months later she is seen for worsening claudication and is scheduled for a femoral-popliteal bypass surgery. She has DM and CKD and is just about the highest risk patient you can imagine. You consult the literature to figure out what to do . . . . .

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**Which of the following is correct about use of enoxaparin in her NSTEMI?**

- A. She’s got a real MI, you should probably give her a little extra (50mg/kg BID)
- B. She is pretty frail, probably best to underdose her a bit (40mg/kg)
- C. Best to give her the right dose.
- D. Enoxaparin? Don’t mess around – this 89yo needs a cath . . . NOW!
Based on recent studies, in her pre-operative management you should:

1. Get a dobutamine echocardiogram and if it is positive, go to cath. If negative, proceed with surgery.
2. Go directly to cardiac catheterization because she is such high risk.
3. Maximize medical therapy and proceed with the vascular surgery.
4. Go do a cardiology fellowship.

Results: DECREASE-V

- Medical treatment in 52 pts
- Revascularization in 49 pts
  PCI in 32 pts, CABG in 17 pts
  75% of patients had either left main or 3 vv. disease

<table>
<thead>
<tr>
<th></th>
<th>Revasc</th>
<th>Medical Tx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death + MI, 30d</td>
<td>42.9%</td>
<td>32.7%</td>
<td>0.30</td>
</tr>
<tr>
<td>Death + MI, 1yr</td>
<td>49.9%</td>
<td>44.2%</td>
<td>0.48</td>
</tr>
</tbody>
</table>

DECREASE-V: Revascularization before major vascular surgery

Question: Is there a benefit to revascularization in the highest-risk pts getting major vascular surgery?

Design: Prospect, RCT of 101 high-risk pts & pos DSE
Revasc vs medical tx before vascular surgery

High-risk: ≥ 3 of: age > 70, angina, prior MI, CHF, DM, CKD, hx stroke

Results: Pre-op revasc in high-risk pts for major vasc surg did not improve outcome

Conclusion: Pt with significant ischemia do not benefit from prophylactic revasc prior to high risk surgery.

Comment: Study was pilot for larger 600 patient study
Suggests prep revasc offers minimal benefit.
Do not extrapolate findings to pts w/ unstable angina.
Based on recent studies, you should:

A. Get a dobutamine echocardiogram and if it is positive, go to cath. If negative, proceed with surgery.
B. Go directly to cardiac catheterization because she is such high risk.
C. Maximize medical therapy and proceed with the vascular surgery.
D. Go do a cardiology fellowship.

Listen, Doc, is there anything we can do to keep her from breaking any bones in the future?” You answer:

A. Sure, she can get some fancy hip protectors – those will work.
B. Two glasses of milk a day – does the body good.
C. She can get an intravenous medication once a year to protect her bones.
D. Calcium and vitamin D.
E. Yeah, uh, don’t fall.

Case Presentation

The patient goes to the OR and does well. One year later you have the chance to care for her again, this time co-managing her on the orthopedic service – while raking leaves she fell and fractured her hip.

She undergoes an uncomplicated R hip arthroplasty. On the day of discharge as you’re preparing the discharge medications, her husband asks some questions, including...

HORIZON: Zoledronic Acid after Hip Fracture

Question: Does zoledronic acid reduce repeat fx and mortality after hip fracture?
Design: 2127 pts w/ hip fracture, within 90d p fx
Random to yearly zoledronic acid v placebo 75% women, all vit D & Ca²⁺

Lyles KW. NEJM. 2007;357:1799-809.
Zoledronic Acid in Hip Fx

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Fracture</td>
<td>8.6%</td>
<td>13.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>Mortality, 1yr</td>
<td>9.6%</td>
<td>13.3%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

NNT = 27

No difference in adverse events including atrial fibrillation

Lyles KW. NEJM. 2007;357:1799-809.

HORIZON: Zoledronic Acid after Hip Fracture

Question: Does zoledronic acid reduce fx and mortality after hip fracture?

Design: Plac-cont, random 2127 pts w/ hip fracture zoledronic acid v placebo yearly;

Results: Zoledronic acid reduces fx and mort if given w/in 90days of hip fx

No difference in side effects

Conclusion: High mortality after hip fx: pts should get bisphosphonate + Ca/vit D

Comment: Consider prescription in hospital, include in discharge summary

Lyles KW. NEJM. 2007;357:1799-809.

"Listen, Doc, is there anything we can do to keep her from breaking any bones in the future?" You answer:

A. Sure, she can get some fancy hip protectors – those will work.
B. Two glasses of milk a day – does the body good.
C. She can get an intravenous medication once a year to protect her bones.
D. Calcium and vitamin D. Done.
E. Yeah, uh, don't fall.
**Short take: Hip protectors**

- Prospective, randomized trial of hip protectors in 1042 nursing home residents showed no protection against hip fracture.
- Growing evidence hip protectors are not helpful.

*HIP PRO. JAMA. 2007;298:413-22.*

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**Summary**

- **Definitely**
  1. Treat osteoporosis in patients after hip fracture.
- **Consider**
  1. Not revascularizing patients prior to surgery unless unstable/would need anyway.
- **STOP**
  1. Giving inappropriate doses of enoxaparin in ACS.

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**Case Presentation**

A 52 year old man with no past medical history presents with acute onset of pleuritic chest pain and shortness of breath. Of note, he sprained his ankle playing basketball 2 weeks prior. On exam he is tachycardic, tachypneic and his chest radiograph is clear.

You suspect a pulmonary embolism. . . .

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**Short Take: Minor injury and VTE**

- A population-based, case-control study with 2,471 patients with VTE showed that VTE was associated with minor injury (OR 3.1). The risk was seen with lower extremity injuries in the 4 weeks before thrombosis.
- Factor V Leiden carriers had a ~50-fold increased risk with a leg injury (OR 49.7).

Short Take: Troponin in acute PE

- A meta-analysis of 20 studies with 1,985 patients found that elevated troponin levels in pulmonary embolism are significantly associated with short-term mortality [OR 5.24 (95%CI: 3.28-8.38)], death from PE [OR 9.44 (95%CI:4.14-21.49)] and adverse outcomes [OR 7.03 (95%CI:2.42-20.43)].
- Probably should check troponin in all patients with PE.


Short Take: CTPA v. V/Q for PE

- Randomized, controlled trial of 1417 patients with high pre-test probability of PE were randomized to CTPA v. V/Q. Both tests showed a similar low rate of PE at 3 month f/u among pts initially without PE (equal tests).
- More PEs detected on CTPA.

Anderson DR. JAMA 2007;298:2743-2753

Case Continued

You decide to order a CT angiogram. The radiologist calls and asks if you want to do anything to prevent contrast nephropathy (his creatinine is 1.5 mg/dL). You pause for a moment, rub your chin, and consider . . . .

Which drug can I give to prevent contrast nephropathy?

A. “Renal dose” dopamine
B. Fenoldopam
C. N-acetylcysteine (NAC)
D. Theophylline
E. None – contrast nephropathy is a disease fabricated by radiologists so they can avoid doing CT scans.

86%
Drugs for prevention of CIN

Question: What is the efficacy of NAC and other agents for reducing CIN?

Design: Meta-analysis of 41 RCTs, 6379 pts
Most with CKD, most > 65yo, most cardiac cath

Agents tested: NAC, theophylline, fenoldopam, statin, dopamine, ascorbic acid, mannitol

CIN: Cr increase > 0.5mg/dL or > 25% w/in 48 hrs

Results


<table>
<thead>
<tr>
<th>Agent</th>
<th>Rate of CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC</td>
<td>Decreased; RR 0.62 (95%CI 0.44-0.88)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Decreased; RR 0.49 (95%CI 0.23-1.06) (NS)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Increased; RR 3.27 (95%CI 1.48-7.26)</td>
</tr>
</tbody>
</table>

Conclusion: Peri-procedural tx with NAC decreased CIN risk; RR 0.62

Comment: Findings support prior studies. No trial has examined dialysis dep or in-hospital morbidity/mortality. Low risk, low cost intervention 600mg PO bid x 2 days

Which drug can I give to prevent contrast nephropathy?

A. “Renal dose” dopamine
B. Fenoldopam
C. N-acetylcysteine (NAC)
D. Theophylline
E. None – contrast nephropathy is a disease fabricated by radiologist so they can avoid doing CT scans.
Case Continued

You decide to give N-acetylcysteine but you’re wondering what else you should do to reduce the risk . . .

Which of the following is correct about preventing contrast-induced nephropathy?

1. Based on the last study, saline + NAC is probably the best way to go.
2. Adding ascorbic acid to saline + NAC helps prevent CIN.
3. Bicarb + NAC is superior to saline + NAC in preventing CIN.
4. N-acetylcysteine (NAC) is fruity and tastes like a fine Napa cabernet.

REMEDIAL

Question: What is the efficacy of bicarbonate versus saline for prevention of CIN?

Design: Prospective, double-blind randomized, 326 pts w/CKD (baseline cr = 2mg/dL), 2 cardiac centers, all getting cath

3 treatment arms pre/post procedure:
- Saline + NAC
- Bicarbonate + NAC
- Saline + NAC + ascorbic acid

CIN: Cr increase ≥ 25% at 48 hrs

Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate of CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + NAC</td>
<td>9.9%</td>
</tr>
<tr>
<td>Bicarbonate + NAC</td>
<td>1.9%</td>
</tr>
<tr>
<td>Saline + NAC + ascorbic acid</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

Absolute RR: Bicarb + NAC vs. Saline + NAC: 8%

NNT = 13
REMEDIAL: Preventing CIN

Question: What is the efficacy of bicarbonate versus saline for prevention of CIN?

Design: Prospective, double-blind randomized, 326 consecutive pts w/CKD, 2 centers

Results: Need to hydrate 13 patients with bicarb to prevent 1 case of CIN

Conclusion: In mod-high risk pts, Bicarb+NAC is superior to saline+NAC. No benefit to vitamin C

Comment: Cardiac cath patients; Bicarb is likely better
Key is moderate to high-risk patients
154mEq/L sodium bicarb in D5W (3 amps) 6ml/kg/h x 1 hr, then 1ml/kg/h x 6 hrs

REMEDIALLY Circ 2007;115:1211-1217

Which of the following is correct about preventing contrast-induced nephropathy?

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B. Adding ascorbic acid to saline + NAC helps prevent CIN.
C. Bicarb + NAC is superior to saline + NAC in preventing CIN.
D. N-acetylcysteine (NAC) is fruity and tastes like a fine wine.

Summary

• Definitely
  1) Order troponins in pts w/acute PE

• Consider
  1) A diagnosis of VTE in patients with recent minor injury of the lower extremity.
  2) Using NAC pre- and post-procedures involving contrast
  3) Using bicarbonate + NAC for pre/post contrast hydration in pts at mod-high risk for CIN

• Definitely
  1) Prescribe either LMWH or UFH tid for VTE prophylaxis in medical patients
  2) Treat severe CDAD with vancomycin PO
  3) Give pneumovax to patients hospitalized with CAP

• Consider
  1) Giving antibiotics for 7 days or less for mild to moderate CAP
  2) Using LMWH instead of UFH for VTE prophylaxis

Update in Hospital Medicine
Summary

- **Definitely**
  1) Treat osteoporosis in patients after hip fracture.

- **Consider**
  1) Not revascularizing patients prior to surgery unless unstable/would need anyway.

- **STOP**
  1) Giving inappropriate doses of enoxaparin in ACS.