New Developments in Inpatient Medicine: Year in Review

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2007

Methods

- Literature review May 2006 - May 2007
- 11 major journals
  - Am J Med
  - Circulation
  - Annals Internal Med
  - Critical Care Medicine
  - ACP Journal Club
  - JAMA
  - Archives Internal Med
  - Lancet
  - BMJ
  - New Engl J Medicine

Selection criteria

- Relevance for inpatient medicine and transitions from inpatient-outpatient
- Potential to change, inform, or confirm practice
- Diverse topics, study types
- (avoid overlap with other course topics)

Topics

- Acute pain
- MSSA bacteremia
- Hypotremia
- Influenza - diagnosis, mortality
- Long-acting beta-agonists
- Preventing venous thromboembolism in medical patients
- Quality - med adherence

Acute pain

- A 28 year old woman with asthma comes to the ED with 3 days R sided abdominal pain, 1 day emesis. LMP 2 weeks ago.
- T=38.5, 90/min, 120/60. Normal cardiopulmonary exam. Abdomen: R lower abd guarding, also tender RUQ. Psoas sign positive. Pelvic and rectal uncomfortable, no acute findings.
- WBC 11,000.

You call a surgeon, who will come in 1 hour to consult. The patient requests "something for the pain" now. Do you:

A. Administer low dose IV morphine
B. Administer morphine IV until the patient is comfortable
C. Administer ketorolac
D. Explain to the patient that the surgeon will be here soon and ask her to wait for analgesia until then
E. Call a different surgeon
Acute abdominal pain
to treat or not to treat...or when to treat

- Common cause of ED visits
  - 40-45% nonspecific
  - 15-30% require surgery
- Treatment of pain prior to diagnosis controversial

Potential effect of opiates on physical examination

- Synthetic opiates inhibit afferent, central, efferent components of pain cycle
  - Voluntary guarding - may decrease if overall pain improves with opiates
  - Involuntary guarding - due to reflex spasm of abdominal wall; unaffected by opiates?
- Net effect on assessment of pain unknown

Do opiates affect the clinical evaluation of patients with acute abdominal pain?

Ranjit et al JAMA 2006;1764

- Study question: What effect do opiates have on the clinical examination in patients with abdominal pain?
  - History
  - Physical examination
  - Clinical management
    - Do opiates delay appropriate surgery?
    - Do opiates prompt unnecessary surgery?
  - Systematic review: 12 studies

- Summary: opiates safe, effective with undiagnosed acute abdominal pain
  - Effect of opiates on clinical evaluation of abdominal pain
    - Opiates do alter physical exam
    - Effect on history unclear
    - No effect on management
  - With improved imaging techniques, accuracy of diagnosis improves, further encouraging liberal analgesia for patients in pain

Effects of opiates on management

- No effect of opiates on management decisions

  Risk of mismanagement

  Change in risk
  Adults +0.3 (-4.1 to +4.7)
  Adult and peds +0.1 (-3.6 to +3.8)

  Opiates decrease risk
  Risk ratio 0 10
  Opiates increase risk

Effects of opiates on history, exam

- History: data inadequate, but blinded clinicians unable to tell which patients received opiate vs. placebo
- Physical exam
  - All studies: 1.55 (1.02-2.36)
  - Studies with adequate analgesia: 2.13 (1.14-3.98)

Summary: opiates safe, effective with undiagnosed acute abdominal pain
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Staph aureus bacteremia in dialysis patients

- Staph aureus bacteremia
  - Common complication of hemodialysis
  - MRSA rates increasing
- Treatment of MSSA: IDSA guidelines
  - Penicillinase-resistant PCN or cephalosporin
  - In practice, Vancomycin commonly continued for MSSA due to convenient dosing

Treatment of MSSA bacteremia

*Styrjewski Clin Infectious Diseases 2007;44:190*

- What are the clinical outcomes for MSSA bacteremia in hemodialysis patients treated with Vancomycin vs. Cefazolin?
  - Prospective study
  - All dialysis patients with MSSA positive blood cultures
  - All patients initially treated with Vanco until susceptibilities available
  - Further Rx per primary team

Clinical outcomes at 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Cefazolin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx failure</td>
<td>0.02</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>0.05</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

B-lactams preferred for MSSA bacteremia in hemodialysis patients

- Independent risk factors for treatment failure
  - Retention of hemodialysis access (odds ratio 5.0, \( p=0.001 \))
  - Vancomycin as principal therapy (OR 3.5, \( p=0.04 \))
- Vancomycin inferior regardless of patient characteristics, comorbidities

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- Quality - med adherence
**Case: part 1**

70 yo man with hypertension, coronary artery disease, asthma, GERD admitted with high fever, cough. Clinical suspicion of pneumonia.
Exam: T=38.5 90/min 130/80  
Euvolemic. Initial serum sodium = 125.

**Question:**

You consider using a new vasopressin receptor antagonist to correct the sodium. Which of the following would lead you to use this therapy for this patient?

A. Seizure  
B. SIADH  
C. CHF  
D. Failure of hypertonic saline to correct sodium  
E. Volume depletion

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**Hyponatremia**

- Most common electrolyte disorder in the hospital
- Significant impact of hyponatremia  
  - Associated with increased mortality with CHF, cirrhosis, neurologic disease  
  - Even mild hypoNa diminishes balance, attention  
- Treatments often nonspecific  
  - Fluid restriction, demeclocycline, lithium

**Vasopressin and hyponatremia**

- Arginine vasopressin (ADH) key contributor to hyponatremia  
  - Regardless of volume status  
- Vasopressin V2-receptor antagonists  
  - Block vasopressin from binding to receptors in distal nephron  
  - Lead to excretion of solute-free water

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**Tolvaptan, a selective vasopressin V2-receptor antagonist, for hyponatremia**

SALT Investigators. NEJM 2006;355:2099

- Purpose: evaluate efficacy and safety of tolvaptan in adults with euvolemic or hypervolemic hyponatremia  
  - CHF, cirrhosis, SIADH  
  - Na < 135 (< 130 in 50%)  
  - 92 sites internationally  
  - 30 day follow up  
- Oral tolvaptan vs. placebo  
  - 15 mg daily (increased to 30, 60 based on Na)  
  - No fluid restriction

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**It works! Tolvaptan effectively raised sodium levels**
**Tolvaptan: adverse effects**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Tolvaptan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirst</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Adverse event: potentially study-related</td>
<td>41%</td>
<td>29%</td>
</tr>
<tr>
<td>Adverse event: serious</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Hyponatremia in first 24 hours</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

**V2-receptor antagonist: a promising treatment for hyponatremia**

- SALT trials: majority of treatment course in outpatient setting
  - Mental functioning better with correction of Na
  - Minimal side effects
- Conivaptan: only vasopressin antagonist approved in US
  - IV for refractory SIADH
- More to come: impact of long term treatment, impact on mortality, oral Rx in U.S.

**Topics**

- Acute pain
- MSSA bacteremia
- Hyponatremia
- **Influenza - diagnosis, mortality**
  - Long-acting beta agonists
  - Preventing venous thromboembolism in medical patients
  - Quality - med adherence

**Case: part 2**

70 yo man with hypertension, coronary artery disease, asthma, GERD admitted with high fever, cough; he looks sick but not critical. Prelim CXR read: atelectasis vs. infiltrate. Blood cultures sent.

Ceftriaxone, azithromycin started. Rapid test for influenza A comes back positive.

**Question**

If the official CXR report is “no acute disease,” which of the following would lead you to continue antibiotics?

A. Patient is improving on antibiotics  
B. I do not trust the CXR report  
C. I do not trust the flu test  
D. IV medications are needed to justify continued hospitalization  
E. I am worried about concomitant bacterial infection

**Influenza in the hospital: testing**

- Rapid testing: 60-95% sensitivity
- Impact of rapid diagnosis of flu in the hospital
  - Infection control
  - Potential antiviral therapy
  - In children, rapid viral testing reduces antibiotic use, testing, hospitalizations
- Does influenza testing in the hospital influence management of adults with pneumonia?
Impact of rapid diagnosis on management of adults hospitalized with influenza

Falsey et al Arch Intern Med 2007;167:354

• Retrospective study of all adults hospitalized with influenza
  – Patients with rapid antigen positive vs. negative or no rapid test sent
  – All had definitive evidence of flu (serologic)
• Stopping antibiotics 7 times more likely with positive rapid test
  – But 61% continued antibiotics

Influenza in the hospital: impact of vaccination

• Influenza virus A and B frequent causes of hospitalization
  – Flu, pneumonia
  – Exacerbation of other chronic illness
• Vaccination reduces mortality, hospitalization
• Limitations of vaccination
  – Under-utilization of vaccine
  – In the elderly, risk of weak immunity or vaccine failure

Influenza vaccination and mortality with community-acquired pneumonia

Spaude Arch Intern Med 2007;167:53

• Are there benefits of influenza vaccine in vaccinated patients hospitalized with pneumonia?
  – Attenuation of disease course (not prevention)
  – Or is the hospitalization a vaccine failure?
• 17,393 patients
  – 34 hospitals, 4 years
  – Vaccinated patients older, sicker; less likely to smoke, live in nursing home

Reduced pneumonia-related deaths after influenza vaccine

In-house all-cause mortality (%)

0 2 4 6 8 10

Vaccinated
Unvaccinated or unknown

All PORT < 4 PORT 4-5 Age < 65 Age > 65

Summary: influenza

• Rapid diagnostic tests reduce antibiotic use
• Prior vaccination associated with lower in-hospital mortality
  – Similar benefit shown with pneumococcal vaccination
• Mechanism of disease attenuation unclear
  – Attenuation of influenza by virus-specific antigens
  – Infection with less virulent pneumonia pathogens
  – Co-receipt of pneumococcal vaccine

Topics

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• Hyponatremia Influenza - diagnosis, mortality
• Long-acting beta agonists
• Preventing venous thromboembolism in medical patients
• Quality - med adherence
Case: part 3

You are aiming to simplify your patient's medication regimen to improve adherence, while at the same time maximizing his care to prevent readmission. He has moderate persistent asthma, and you wonder whether to add a long acting steroid to his salmeterol, or whether to change the salmeterol to another medication.

Long-acting beta-agonists in asthma

- Moderate-severe persistent asthma - NIH guidelines
  - Inhaled corticosteroid
  - Long-acting inhaled beta-agonist
- Beta-agonist controversies
  - Tolerance
  - Worsened disease control
  - Reports to FDA of deaths with Salmeterol

SMART: Salmeterol multicenter asthma research trial

Post-marketing study of 26,355 patients

<table>
<thead>
<tr>
<th>Resp deaths</th>
<th>Asthma deaths</th>
<th>Resp death or near-death in AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>RR 2.2</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>RR 4.4</td>
<td></td>
</tr>
</tbody>
</table>

Nelson Chest 2006;129:15

Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and deaths

Salpeter Ann Intern Med 2006;144:904

19 trials with 33,826 patients

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations for asthma</td>
</tr>
<tr>
<td>Life-threatening asthma exacerbations</td>
</tr>
</tbody>
</table>

Favors B-agonist |

Favors placebo |

Long-acting beta-agonists increase risk of bad outcomes with asthma

- Increased exacerbations, deaths
- Limitation: placebo group used short acting beta-agonists
- Inhaled steroid attenuate, don’t eliminate risk
- What to do:
  - Use inhaled steroids first
  - Reserve long acting beta-agonists for refractory symptoms
  - Consider anticholinergics

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Case: part 4
You consider your patient’s risk of developing DVT or PE. He is ambulatory at baseline but not currently due to his acute illness. Which of the following do you recommend?
A. Ted hose to reduce DVT
B. Unfractionated or LMW heparin to reduce fatal PE
C. LMWH to reduce mortality
D. No prophylaxis indicated unless he has CHF or cancer

Preventing VTE in Medical Patients: Meta-analysis of outcomes with anticoagulation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>0.43 (0.26-0.71)</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.38 (0.21-0.69)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>0.47 (0.22-1.00)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.97 (0.79-1.19)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.32 (0.73-2.37)</td>
</tr>
</tbody>
</table>

Dentati Ann Intern Med 2007:146:278

Preventing DVT in Medical Patients

- UFH or LMWH effective
  - 60% risk reduction in DVT, PE
  - Borderline decrease in hemorrhage with LMWH
- Target high risk patients
  - CHF
  - Severe respiratory disease
  - Bedridden plus additional risk factor
- Consider compression hose for low risk patients

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Case: part 5
Your 70 year old patient who presented with lower respiratory tract infection and was diagnosed with influenza is now ready for hospital discharge. His discharge medications are aspirin, atorvastatin, metoprolol, amlodipine, omeprazole, enalapril, albuterol, fluticasone.

As his care is handed off from the inpatient physician to the primary care physician, what are the risks of a medication problem?

Question

A. None - you explained the regimen to him yourself
B. He has close primary care followup so he should be fine until his clinic appointment
C. You are fine because of your system to meet the JCAHO Patient Safety Goal to obtain and document the patient’s medications on admission and discharge
D. The risk is real and a medication discrepancy or non-adherence would increase his risk of readmission and mortality
Medication Nonadherence

- Transitions of care are a high risk time
  - Hospital discharge: discontinuity between inpatient and outpatient MD’s
  - Changes in patients’ medical status and medications
- Quality improvement efforts increase proportion of patients discharged on evidence-based therapies
  - Do patients adhere to medication regimen?
  - How does nonadherence impact outcomes?

Impact of medication discontinuation on mortality after MI
Ho Arch Intern Med 2006;166:1842

Study goals
1. Evaluate rates of ASA, B-blocker, statin use at hospital discharge after acute MI, and 1, 6, 12 months post-discharge
2. Identify patient and MI treatment factors associated with med nonadherence
3. Correlate nonadherence with 1 and 12 month mortality

Impact of medication discontinuation on mortality after MI

<table>
<thead>
<tr>
<th>Status at 1 year</th>
<th>1 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking all 3 meds</td>
<td>98%</td>
</tr>
<tr>
<td>Taking 1 med</td>
<td>96%</td>
</tr>
<tr>
<td>Taking 0 meds</td>
<td>89%</td>
</tr>
</tbody>
</table>

Risk of death:
- stop ASA: 1.82
- stop B-blocker: 1.96
- stop statin: 2.86

Implications of medication discontinuation

- Demographic factors predicted higher risk of nonadherence
  - Elderly, women, lower education
- Mortality impact of non-adherence is high - may reflect poor self-care in general
- Quality efforts should focus on the transition from inpatient to outpatient, with careful medication reconciliation at the first post-discharge visit

Take Home Points

- Acute pain: opiates do alter physical exam with negligible effect on management
- MSSA bacteremia in hemodialysis patients: treat with beta-lactams
- Hyponatremia: consider vasopressin antagonists for euvolemic, hypervolemic hyponatremia
- Influenza: use rapid diagnostic testing to decrease antibiotics use; vaccinate to attenuate severity of pneumonia
Take Home Points

- Long acting inhaled beta-agonists in asthma: use inhaled steroids first
- Preventing VTE in medical patients: prophylaxis with heparin for patients to reduce incidence of thrombosis and PE-related mortality
- Medication nonadherence: focus quality efforts on adherence after hospital discharge to improve patient outcomes