Inpatient Internal Medicine Update
A Patient-Centered Review of the Literature

A. Scott Keller
October 28, 2016
Objectives

• Discuss the latest studies on duration of therapy for community-acquired pneumonia.

• Understand the new Sepsis-3 definitions (and controversy) for sepsis and septic shock.

• Learn the association between COPD and pulmonary emboli.

• Review the new ACCP guidelines for VTE.
The Hospital Saga of Mr. Lucky
Mr. Lucky

- 75 year old with mod COPD, CKD, provoked DVT in 1990, and UGI bleed one year ago.
- He comes to the ED: “I can’t stop coughing.”
- T 37.4°C, BP 110/70, HR 100, RR 20, SaO₂ 94% on room air.
- Hgb 13.5 g/dL, WBC 14 x 10³/μL, Na 135 mmol/L, glc 100 mg/dL, ABG 7.38/70/38 on room air, BUN 16 mg/dL, creat 1.5 mg/dL, lactate 1.6 mmol/L (normal ≤2.3).
- Chest x-ray shows...
Right Lower Lobe Pneumonia
How sick is he?

- Pneumonia Severity Index (PORT Score) = 85 (Class III, mortality 0.9%).
- Started on oral levofloxacin 750 mg q24 hours for community-acquired pneumonia (CAP) and prophylactic enoxaparin.
- Does he even need to be admitted?

“Among hospitalized patients who received fluoroquinolones for CAP, there was no association between initial route of administration and outcomes.”

Question #1

What is the appropriate duration of therapy to treat CAP?
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What is the appropriate duration of therapy to treat CAP?
A. Five days.
B. Seven days.
C. Eight days.
D. 10-14 days.
Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomized Clinical Trial

Background

• CAP is a leading cause of morbidity and mortality worldwide\textsuperscript{1} and appears to be the leading cause of sepsis.\textsuperscript{2}

• IDSA/ATS guidelines recommend a 5-day course of antibiotics, but providers routinely give longer treatment.

• Multicenter RCT to assess if duration of antibiotic based on IDSA/ATS criteria is as effective as conventional treatment.

• 1. WHO: The top ten causes of death. \url{http://www.who.int/mediacentre/factsheets/fs310/en}
Study Design

- Hospitalized patients diagnosed as having CAP were recruited from January 1, 2012, through August 31, 2013.

- Intervention group treated with antibiotics for minimum of 5 days (determined by provider).

- Antibiotic stopped at this point if temp ≤ 37.8°C or less for 48 hours and no more than 1 CAP-associated sign of clinical instability:
  - SBP < 90 mmHg
  - HR > 100/min
  - RR > 24/min
  - Arterial O₂ < 90% or PaO₂ < 60 mm Hg (room air).
Study Design

• Primary outcomes were clinical success rate at day 10 and late follow-up (day 30) since admission.

• “Clinical success” defined as resolution or improvement in signs and symptoms related to pneumonia without further antibiotics, and CAP-related symptoms at day 10 measured with the 18-item CAP symptom questionnaire.
IDSA/ATS Guidelines

- Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy (level II evidence). (Moderate recommendation.)

- Longer duration of therapy may be needed if initial therapy not active against the identified pathogen or if complicated by extrapulmonary infection, such as meningitis or endocarditis. (Weak recommendation; level III evidence.)

Findings

• After randomization and exclusions, 137 patients in control group (mean PSI = 83.7) and 146 in intervention group (mean PSI = 81.8).

• Control patients had mean duration of antibiotic for 10 days vs 5 days for intervention patients ($P<0.001$).

• 9 control patients vs 2 intervention patients readmitted by day 30 ($P=0.02$).

• No difference in any other parameter including mortality, recurrence, complications, adverse effects, or LOS.
Findings

<table>
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<tr>
<th>Clinical Success (%), Per-Protocol Analysis</th>
<th>Controls</th>
<th>Intervention</th>
<th>$P$-Value</th>
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<tbody>
<tr>
<td>10 Days</td>
<td>50.4</td>
<td>56.3</td>
<td>0.12</td>
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<tr>
<td>30 Days</td>
<td>92.7</td>
<td>94.4</td>
<td>0.54</td>
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</table>

<table>
<thead>
<tr>
<th>Clinical Success (%), Intention-To-Treat Analysis</th>
<th>Controls</th>
<th>Intervention</th>
<th>$P$-Value</th>
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</thead>
<tbody>
<tr>
<td>10 Days</td>
<td>48.6</td>
<td>56.3</td>
<td>0.18</td>
</tr>
<tr>
<td>30 Days</td>
<td>88.9</td>
<td>91.9</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Cautions

• Almost 80% of patients received quinolones.

• Few patients were included who had severe disease (PSI class V). There were 61 and 60 patients grouped as PSI IV-V in control and intervention groups, respectively.

• Patients requiring ICU care were excluded.
• Stopping antibiotic treatment based on clinical stability criteria after a minimum of 5 days of appropriate treatment is not inferior to traditional treatment schedules in terms of clinical success.

• The authors concluded that IDSA/ATS guidelines concerning duration of antibiotic treatment can be safely implemented among hospitalized patients with CAP.
Total Duration of Antimicrobial Therapy in Veterans Hospitalized with Uncomplicated Pneumonia: Results of a National Medication Utilization Evaluation

Study Design

- Retrospective multicenter evaluation in 30 VHA facilities.
- Manual review of electronic medical records of inpatients discharged with uncomplicated CAP or HCAP.
- Appropriate CAP therapy duration was at least 5 days, and up to 3 additional days beginning the first day of clinical stability criteria.
- Appropriate HCAP therapy duration defined as 8 days.
Findings

• Study included 1195 patients with CAP and 544 with HCAP.

• Only 13.9% of patients (CAP 6.9%, HCAP 29.0%) received therapy duration consistent with guidelines!

• Median therapy was 4 days (inpatient IV), 1 day (inpatient PO), and 6 days (outpatient PO).

• Therapy duration not associated with readmission or mortality rate.

• CDI was rare (15 cases), but more common in guideline therapy (40.0% vs 13.6%, P<0.01).
Cautions

• Retrospective study performed at VHA facilities, predominantly male patients.
The Bottom Line

• Patients with uncomplicated pneumonia were commonly prescribed antimicrobials for the duration of therapy in excess of guideline recommendations.

• Approximately half of all therapy was prescribed upon hospital discharge—possible opportunity for improvement using antimicrobial stewardship programs.
Recap of Question #1

What is the appropriate duration of therapy to treat CAP?

A. Five days.
B. Seven days.
C. Eight days.
D. 10-14 days.
My Opinion

Treat CAP with antibiotics per guidelines.

Opportunity for quality improvement in hospitals.

Make sure patients are up to date with pneumonia and influenza vaccines!
Back to Mr. Lucky...
Oops!
• Four hours after admission, he develops fever (T 39.0°C) with shaking chills/rigors.
• BP 90/40, HR 120, RR 36, SpO₂ 84% room air.
• The Rapid Response Team is called.
He's transferred to the ICU.
“Are you part of the rabbit response team?”
Question #2

Which of these patients has/have sepsis?
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Which of these patients has/have sepsis?
A. Mr. Lucky (T 39.0, HR 120, and CXR).
B. Mr. Lucky (RR 36, WBC 14,000, and CXR).
C. Mr. Lucky’s roommate who has acute delirium, BP 96/50, and RR 24.
D. Mr. Lucky’s doctor, who has a cold and just ran up 3 flights of stairs to assess him.
E. All of the above.
F. It depends on your definition of sepsis.
“Sepsis is not a specific illness but rather a syndrome encompassing a still-uncertain pathobiology.”


• “The systemic response to infection.”

• “The clinical syndrome defined by the presence of both infection and a systemic inflammatory response.”

• “The presence (probable or documented) of infection together with systemic manifestations of infection.”

Original Sepsis Definitions

- Two or more SIRS criteria (1991)
  - WBC >12,000 or <4,000 or >10% bands.
  - T <36 or >38.3°C.
  - HR >90.
  - Hyperventilation (RR >20 or PaCO$_2$ <32 mmHg).

- Additional SIRS criteria (incorporated 2001, revised 2012)
  - General variables such as altered mental status plus inflammatory, hemodynamic, organ dysfunction, and tissue perfusion variables.
Problem

• SIRS is nonspecific and may occur from infection OR noninfectious conditions like pancreatitis, autoimmune disorders, vasculitis, thromboembolism, burns, or surgery.

• Running up stairs can give you 2 SIRS criteria!
Problem

• Recent study of 109,663 patients with severe sepsis (infection and organ failure) found 13,278 (12.1%) had SIRS-negative (<2 SIRS criteria) severe sepsis.8

• “The SIRS criteria do not necessarily indicate a dysregulated, life-threatening response.”9

• SIRS may simply reflect an appropriate host response that is frequently adaptive.”9

Enter the Latest Definitions: Sepsis-3

*JAMA* February 23, 2016
Sepsis-3 Task Force Issues

• Differentiate sepsis from uncomplicated infection.
• Update definitions of sepsis and septic shock.
• Develop clinical criteria that could better identify patients with suspected infection likely to progress to a life-threatening state.
New **Sepsis** Definition

- “Life-threatening organ dysfunction caused by a dysregulated host response to infection.”

- Organ dysfunction can be identified as acute change in SOFA score $\geq 2$ due to the infection.

- SOFA score gives 0-4 points for each of 6 variables: PaO$_2$/FiO$_2$ ratio, MAP/vasopressor use, GCS, serum creatinine or urine output, total bilirubin, platelet count—higher score correlates with higher mortality.
qSOFA for Non-ICU Patients

- For non-ICU patients with infection, screen for possible sepsis with 2 or more qSOFA criteria:
  - Altered mentation.
  - RR $\geq 22$/min.
  - SBP $\leq 100$ mmHg.

- Score of $\geq 2$ associated with poor outcomes due to sepsis—consider possibility of sepsis.

Can be rapidly scored at bedside--
No need for blood tests!
New Septic Shock Definition

• “A subset of sepsis in which underlying circulatory, cellular/metabolic abnormalities are profound enough to substantially increase mortality.”

• No more “severe sepsis.”
Clinical Criteria to Identify Septic Shock

- Hypotension requiring vasopressor therapy to maintain MAP ≥ 65 mmHg

  And

- Having a serum lactate level > 2 mmol/L after adequate fluid resuscitation.

This combination is associated with hospital mortality rates greater than 40%!
Patient with Suspected Infection

qSOFA ≥2?
- No → Sepsis Still Suspected?
  - No → Monitor Clinical Condition, Reassess for Possible Sepsis if Indicated
  - Yes → Yes

- Yes → Assess for Evidence of Organ Dysfunction
  → SOFA ≥2?
    - No → Yes
    - Yes → Sepsis

Despite Adequate Fluid Resuscitation,
1. Vasopressors to maintain MAP ≥ 65 AND
2. Lactate ≥2?

- No → No
- Yes → Septic Shock

Yes
Recap of Question #2

Which of these patients has/have sepsis?

A. Mr. Lucky (T 39.0, HR 120, and CXR).
B. Mr. Lucky (RR 36, WBC 14,000, and CXR).
C. Mr. Lucky’s roommate who has acute delirium, BP 96/50, and RR 24.
D. Mr. Lucky’s doctor, who has a cold and just ran up 3 flights of stairs to assess him.
E. All of the above.
F. It depends on your definition of sepsis.
So what’s the catch?
Severe Sepsis/Septic Shock Early Management Bundle (SEP-1)

• New CMS Core Metric (NQF #0500) for discharges on or after October 1, 2015.
• Applies to patients with severe sepsis and septic shock.
Severe Sepsis/Septic Shock Early Management Bundle (SEP-1)

To establish severe sepsis, all 3 of the following must be met within 6 hours of each other:

• Documentation of a suspected source of infection.

• Two or more SIRS criteria.

• Evidence of organ dysfunction.
CMS Response July 26, 2016

• “A change to the existing definition could disrupt the 15-year trend toward further reduction in sepsis mortality.

• Prior to changing the widespread and understood definitions used in SEP-1, rigorous clinical investigation will be required of the task force’s proposed definitions.

• In the coming years, CMS will track the research and field testing that the proposed definitions will inspire.”

So What Do We Do Now?
Early Recognition of Sepsis is Key!

- A constellation of clinical, laboratory, radiologic, physiologic, and microbiologic data generally required to diagnose sepsis and septic shock.

- The new definitions are **not** diagnostic of sepsis since they do not include specific criteria to identify infection.

- qSOFA can help identify non-ICU patients at risk for dying from sepsis, but needs prospective validation.

11. R Neviere, UpToDate 3/17/16.
But…

- These new definitions have not yet been incorporated into practice guidelines, so still use the “original” definitions of sepsis, severe sepsis, and septic shock.

- A non-ICU patient with suspicion of infection and ≥ 2 qSOFA criteria should be evaluated and treated with heightened concern for sepsis.

12. Personal communication, Dr. Ognjen Gajic, Professor of Medicine (Critical Care), Mayo Clinic.
Treatment

• Call RRT if patient meets criteria → ICU.

• Otherwise if concern for sepsis:
  • Draw cultures, lactate, and start empiric antibiotics.
  • Fluid challenge if sepsis-induced tissue hypoperfusion and suspicion of hypovolemia for minimum of 30 mL/kg of crystalloids.
  • Imaging to identify source.
  • If persistent hypotension or high lactate → ICU.

12. Personal communication, Dr. Ognjen Gajic, Professor of Medicine (Critical Care), Mayo Clinic.
Recognize sepsis—difficult, but multiple clinical parameters can help do this.

Treat sepsis promptly! May require transfer to ICU.
I DON'T ALWAYS GET SUCKED INTO A JET ENGINE.

BUT WHEN I DO, I USE ICD 10 CODE V97.33XD.

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Back to Mr. Lucky…
In the ICU…

• Mr. Lucky is initially given vancomycin and cefepime in addition to levofloxacin.

• He fortunately has a rapid recovery and does not require intubation.

• Blood and sputum cultures remain negative and antibiotics are de-escalated back to levofloxacin alone.

• He remains stable and is transferred back to the medicine service in two days.
Oops!
Acute Change in Clinical Status

- Mr. Lucky develops worsening dyspnea, but no cough, sputum, or wheezing. He tells his nurse “my chest hurts when I take a deep breath.” No orthopnea or leg edema.

- Vital signs show temp 37 °C, BP 110/60, HR 102, RR 22, SaO₂ 91% on room air.

- Labs show normal WBC, negative troponin.

- Your visiting medical student wonders about a COPD exacerbation and starting steroids.

- You mention a new study…
Question #3

What is the next best intervention?
Question #3

What is the next best intervention?
A. Start IV methylprednisolone 125 mg q6h x 5 days.
B. Check a BNP.
C. Check a D-dimer.
D. Obtain a chest CT angiogram with PE protocol.
Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A Systematic Review and Meta-Analysis

• FE Aleva, LWLM Voets, SO Simons, Q de Mast, AJAM van der Ven, et al.
• *Chest* published online August 2016.
Background

• The majority of AECOPD develop in response to infections, but in about 30% of cases no clear etiology is found.

• Prior population studies have shown either a modest excess risk for PE with OR ranging from 2.51 (CI, 1.62-3.87) to 5.46 (CI, 4.25-7.02) or no association at all.
Study Design and Findings

- Systematic search of MEDLINE and EMBASE from 1974 to October 12, 2015. Of 1650 identified studies, 7 (880 patients) were included for the analysis.

- **16.1%** of patients had PE (32.5% had isolated subsegmental PE) and 10.5% had DVT.

- In patients with AECOPD who had a PE, pleuritic pain was reported more frequently as were signs of cardiac failure like hypotension, syncope, and acute right failure.

- Signs of RTI were less common in PE.
Cautions

• Heterogeneity of findings among studies (prevalence rates of PE ranging from 3.3% to 29.1%).

• Risk of publication bias.

• Predominately male patients.
The Bottom Line

• PE is frequently seen in unexplained AECOPD. Two-thirds of emboli are found in larger arteries that have a clear indication for anticoagulant treatment.

• “PE should receive increased awareness in patients with unexplained AECOPD, especially when pleuritic chest pain and signs of cardiac failure are present and no clear infectious origin can be identified.”
What next?

- Based on low suspicion for AECOPD, you do not start steroids (which would be given as oral prednisone 40 mg daily for 5 days).\(^{14}\)
- Since no HF symptoms, you forego a BNP.
- You choose not to obtain a D-dimer since Mr. Lucky has a high pre-test probability for PE.\(^{15}\)
- You start N-acetylcysteine and IV normal saline and get a CT.


Chest CT

- Resolving right lower lobe pneumonia.
- No new areas of pneumonitis or interstitial edema.
- Bibasilar atelectasis.
- But...there are 2 tiny subsegmental PEs.
- You get a bilateral lower extremity US that is negative for DVT.
Now what do we do?

- Presumed provoked PE while in hospital despite prophylactic enoxaparin.
- Prior provoked DVT in 1990 after traveling, treated with 3 months of warfarin, no recurrence.
- History of upper GI bleed (NSAID use) one year ago.
- Should we start anticoagulation?
New VTE Guideline!
Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report

New Recommendations

• In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a
  • (i) low risk for recurrent VTE, we suggest clinical surveillance over anticoagulation (Grade 2C)
  • (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (Grade 2C).

Or

• (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (Grade 2C).
The Plan

- Careful discussion of benefits and risks (shared decision making) with Mr. Lucky and his family.
- He remains stable and does not require oxygen.
- He is easily and frequently ambulatory in the hospital and expects to dismiss tomorrow.
- He prefers to avoid starting anticoagulation and you agree this is reasonable, but you suggest a repeat LE US in 5-7 days.
- You continue prophylactic enoxaparin while he is in the hospital.
Additional New ACCP Recommendations

• *2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).
Additional New ACCP Recommendations

• *3. In patients with DVT of the leg or PE and cancer (“cancer-associated thrombosis”), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).

• *18. In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).
Additional New ACCP Recommendations

• *20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2B).

• *22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B).
**Additional New ACCP Recommendations**

- **23.** In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

- **29.** In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).
Additional New ACCP Recommendations

• *30. In patients who have recurrent VTE on long term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).
Recap of Question #3

What is the next best intervention?
A. Start IV methylprednisolone 125 mg q6h x 5 days.
B. Check a BNP.
C. Check a D-dimer.
D. Obtain a chest CT angiogram with PE protocol.
For patients who have unexplained AECOPD, look for PE!

Keep the new ACCP guidelines or your iPad!
Summary

• In patients with CAP, a 5-day course of antibiotics is appropriate, assuming clinical stability.

• The new sepsis definitions and clinical criteria are another tool to help identify patients likely to have sepsis and septic shock, but continue using the current SIRS criteria for patient care, documentation, and billing.

• Early recognition and treatment of sepsis is key!
Summary

• In patients who have unexplained AECOPD, consider checking for PE.

• Learn the new ACCP guidelines for VTE treatment recommendations.
A Happy Ending!
Acknowledgement

Thanks to the ACP Hospitalist Weekly staff for their outstanding work to keep hospitalists updated on the current literature!

- Stacey Butterfield
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- Mollie Durkin
ACP Hospitalist® Weekly

Welcome to this week’s issue of ACP Hospitalist Weekly, an update for hospitalists published every Wednesday by the American College of Physicians.

IN THE NEWS FOR THE WEEK OF MARCH 23, 2016

Oxygen therapy

Reintubation rates lower with noninvasive ventilation or high-flow oxygen than standard therapy

The results of these 2 studies add to the accumulating evidence that noninvasive approaches have a role in reducing respiratory failure and need for reintubation, according to an accompanying editorial. More...

ICU care

Diagnoses of Medicare ICU patients have shifted

Cardiovascular disease remains the top disease category of primary diagnoses, but it declined yearly from 1996 to 2010, while infection-related diagnoses, especially sepsis, rose. More...
Thank you for your attention!

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