Community-Acquired Bacterial Pneumonia: Is There Anything New?

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Disclosure:
Dr. Liu discloses that he is on the advisory board for Cempra and Daiichi Sankyo

CME:

Learning Objectives
After participating in this activity, the primary care physician will be able to:
• Describe trends in the microbiology of community-acquired pneumonia in the United States and the impact on clinical outcomes
• Select evidence-based empiric antibiotic therapy based on national susceptibility trends and ideally on local patterns
• Initiate broad-spectrum antibiotic therapy in appropriate patients
• Modify therapy in patients who don’t respond to initial antibiotic therapy
• List medications on the horizon for community-acquired bacterial pneumonia
Following an episode of CABP, it takes an adult age ≥50 years an average of ___ days to achieve full productivity.

1. 9
2. 15
3. 21
4. 27

Retrospective analysis of adults with CAP initially managed in a primary care clinic showed all of the following to predict non-responsiveness except:

1. Bilateral rales
2. Former smoker
3. Initial presentation to urgent care
4. Myalgia

Several systematic reviews and meta-analyses since 2007 show which of the following is preferred as initial empiric therapy in the outpatient management of CABP?

1. Macrolide
2. β-lactam + macrolide
3. β-lactam + respiratory fluoroquinolone
4. There is no preferred empiric therapy as the data are inconsistent
Only 2 Antibiotics Approved for Community-Acquired Bacterial Pneumonia Since 2007

Tigecycline  
(2009)

Ceftaroline fosamil  
(2010)

Both are injectable antibiotics

So is there really anything to talk about?  
Yes!
Overview

- Epidemiology of community-acquired pneumonia
  - Still significant cause of morbidity and mortality
  - Costs and hospital length of stay are concerns
  - New diagnostic tests for wider array of pathogens
  - Pathogen susceptibility continues to change
  - New definition of community-acquired bacterial pneumonia
  - Collateral damage driving therapeutic change
  - New antibiotics on the horizon

Case Study

- RD is a 59-year-old male who presents to his primary care physician with dyspnea on exertion and cough
- History, physical examination, and chest X-ray suggest a diagnosis of community-acquired bacterial pneumonia
- A macrolide antibiotic is prescribed pending laboratory confirmation
- Four days later, RD returns complaining of continued symptoms that now include fever
- Do you admit or treat as an outpatient?
- If treated as an outpatient,
  - Do you culture?
  - What antibiotic(s) do you start?
  - What do you do if he doesn’t get better?

Epidemiology and Burden

- Incidence
  - 950,000 cases/year in adults age <65 y
  - 1.3 million cases/year in adults age ≥65 y
  - Incidence has declined since introduction of PCV13
    - 3y prospective study of nearly 1 million pediatric ED visits
    - Incidence of CAP decreased 16%
    - Incidence of pneumococcal CAP decreased 63%
    - 28,575 episodes: 72% managed as outpatient
    - Episode length: 31.8 d (inpatient), 10.2 d (outpatient)
    - Cost (all-cause total)
      - Inpatient: $11,148 to $51,219
      - Outpatient: $1,048 to $5,613

Epidemiology and Burden (cont)

- In adults age ≥50 y
  - Time to resolution of symptoms >3 weeks
  - Absenteeism 13 days
  - 21 days before achieving full productivity
  - 8th leading cause of death* and leading cause of infection-related death in U.S.²
- Persons with CAP have a greater risk of 10-year mortality vs controls (hazard ratio 1.65³)

*Pneumonia and influenza combined

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Etiology of CAP

- No pathogen detected
- Bacterial only
- Viral-viral
- Fungal or mycobacterial
- Bacterial-viral (3%)


N=2259 adults hospitalized with radiographic evidence of CAP in 5 U.S. hospitals, January 2010 through June 2012

Etiology of CAP (cont)

- Multiple pathogen
- Single pathogen
- No pathogen detected


N=2259 adults hospitalized with radiographic evidence of CAP in 5 U.S. hospitals, January 2010 through June 2012
Macrolide-resistant S. pneumoniae, United States, 2012


Although the number of isolates is small (N=91), it shows the wide geographic variability in susceptibility of M. pneumoniae to a macrolide.

City (number of M. pneumoniae respiratory isolates tested)
Collection period: August 2012 – April 2014
Etiology of CABP

Does not include viruses, fungi, etc.

Common bacteria
- S. pneumoniae
- H. influenza
- S. aureus
- Group A streptococci
- M. catarrhalis

‘Atypical’ bacteria
- C. pneumoniae
- M. pneumoniae
- L. pneumophila

Other
- Community-associated MRSA
- Gram-negative bacilli
  - E. coli
  - Ps. aeruginosa

Definition of CABP

- Acute bacterial infection of the pulmonary parenchyma
- Associated with chest pain, cough, sputum production, difficulty breathing, chills, rigor, fever, or hypotension
- Accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph
- Acquired in the community vs hospital or healthcare facility

A patient with a Pneumonia Severity Index of II

1. Can be managed as an outpatient
2. Should be admitted to the ICU
3. Has an average mortality rate of 7%
4. Is most likely infected with a Gram-negative pathogen

Comparison of Care Recommendations Based on PSI vs CURB-65 Scores

<table>
<thead>
<tr>
<th>PSI Risk Class</th>
<th>No. of Points</th>
<th>% Mortality</th>
<th>Recommended Site of Care</th>
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</thead>
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<tr>
<td>I</td>
<td>&lt; 7</td>
<td>0.1</td>
<td>Outpatient</td>
</tr>
<tr>
<td>II</td>
<td>7-20</td>
<td>0.6</td>
<td>Outpatient</td>
</tr>
<tr>
<td>III</td>
<td>21-40</td>
<td>2.8</td>
<td>Outpatient or brief inpatient</td>
</tr>
<tr>
<td>IV</td>
<td>41-100</td>
<td>8.2</td>
<td>Inpatient</td>
</tr>
<tr>
<td>V</td>
<td>&gt;100</td>
<td>29.2</td>
<td>Inpatient; consider ICU</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CURB-65 Score</th>
<th>0 or 1</th>
<th>2 or 3</th>
<th>&gt;3</th>
<th>Likely Suitable for Home Treatment</th>
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<tbody>
<tr>
<td>2</td>
<td>&lt;3</td>
<td></td>
<td></td>
<td>Likely suitable for home treatment</td>
</tr>
<tr>
<td>3-5</td>
<td></td>
<td></td>
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</tbody>
</table>

*Absence of risk factor; †Options may include short inpatient stay or as hospital-supervised outpatient; ‡Assess for ICU admission, especially if CURB-65 score = 3


Limited Value of Signs and Symptoms in Determining Etiology

Limited Association of Common Comorbidities with Etiology

Molecular Testing vs Culture Improves Pathogen Detection

Bars are percentages of cases with a positive test result relative to the number of cases with a valid test.

Outpatient Treatment, 2007

- Previously healthy and no risk for drug-resistant S. pneumoniae
  - Macrolide
  - Doxycycline
- Presence of comorbidities or other risks for drug-resistant S. pneumoniae
  - Respiratory fluoroquinolone
  - β-lactam + macrolide
- High rate (>25%) of macrolide-resistant S. pneumoniae (MIC ≥16 mcg/mL)
  - Respiratory fluoroquinolone, ceftriaxone, cefpodoxime, cefuroxime, doxycycline

Monotherapy vs Combination Therapy

- β-lactam vs β-lactam/macrolide
  - β-lactam vs β-lactam/macrolide vs FQ
- FQ vs β-lactam/macrolide
- FQ vs macrolide vs FQ/β-lactam vs macrolide/β-lactam
- Macrolide vs non-macrolide

Similar outcomes and no clear best regimen for empiric therapy.
Collateral Damage

- Typically refers to ecological adverse effects of antibiotic therapy
- Specifically, the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms
- Should it also include other unintended, serious consequences of antibiotic therapy?
  - Fluoroquinolone-tendinopathy, QTc prolongation
  - Macrolide-hepatotoxicity, QTc prolongation


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Factors Associated with Non-Responsive CAP in Primary Care

- Retrospective analysis of 250 adults with CAP initially managed in primary care clinic
- 85 cases (ie, non-responsive), 165 controls
- Non-responsive CAP was defined as worsening symptoms after 4 days or no improvement within 10 days of starting antibiotic therapy
- In the 85 cases at initial visit:
  - 80% had a chest X-ray, 3% additional testing
  - Initial treatment: macrolide (33%), quinolone (33%), no antibiotic (11%), amoxicillin/amoxic-clav (6%)
- Factors predicting non-responsiveness
  - Former smoker (odds ratio 2.27)
  - Initial presentation to urgent care (odds ratio 2.10)
  - Myalgia (odds ratio 2.79)

What is the “state of the art” in CAP/CABP Management?

- Suspect diagnosis based on symptoms
- Know risk factors for poor outcome (clinical: PSI, CURB-65)
- Send labs: CBC, CMP, CXR, sputum or other cultures
- Outpatient management or admit to hospital?

Choose antibiotics:

- No antimicrobial (healthy host, viral, likely self-limited)
- Narrow (macrolide?) if viral vs. mycoplasma (but resistance?)
- Narrowish (amox-clav, TMP-SMX)
- Broad-spectrum (fluoroquinolone or macrolide + beta-lactam)

- If patient not improving:
  - Broaden further (vancomycin, 3rd generation-cephalosporin, carbapenem ???)
  - Perform diagnostic procedure
  - Broader Rx, hospital stay ⇒ more “collateral damage”

Antibiotics on the Horizon

- Cethromycin - ketolide
- Omadacycline - tetracycline
- Sitafloxacin - fluoroquinolone
- Lefamulin - pleuromutilin
- Solithromycin - fluoroketolide

Cethromycin

- Oral ketolide
- Potent activity against S. pneumoniae
- FDA denied approval in 2009

Review used updated efficacy standards

- 2 Phase III studies vs clarithromycin in mild/moderate CAP with clinical cure rates (ITT) of
  - CL05-001 (N=584): 83.1% vs 81.1%
  - CL06-001 (N=522): 82.9% vs 88.5%

**Omadacycline**

- Oral and IV tetracycline
- Potent activity against resistant Gram-positive bacteria, including *S. pneumoniae* and MRSA
- Comparable to tigecycline
- Good oral bioavailability
- No significant nausea/vomiting


**Sitafloxacin**

- Oral fluoroquinolone
- High activity against *S. pneumoniae, ESBL-producing E. coli* and *K. pneumoniae*
- 7 days of treatment resulted in clinical improvement (94.2%) and bacteriologic cure (95.4%) in *S. pneumoniae* CABP (N=72)
- Photosensitivity in Caucasians a concern


**Lefamulin**

- Oral and IV pleuromutilin antibiotic
- Potent activity against multi-drug-resistant strains of *S. pneumoniae*
- macrolide-sensitive and macrolide-resistant *M. pneumoniae*
- Granted qualified infectious disease product/fast track status by FDA
- LEAP2 study- comparison with moxifloxacin in moderate CABP (in progress)

**Solithromycin**

- Oral and IV floroketolide
- Highly active against
  - macrolide-resistant S. pneumoniae\(^1,2\)
  - M. catarrhalis\(^2\)
- 2-fold less active than azithromycin against H. influenzae\(^2\)
- Good activity against S. aureus, including MRSA\(^2\)
- In patients with moderate/moderately severe CABP, solithromycin demonstrated non-inferiority vs levofloxacin\(^3\) and moxifloxacin\(^4\) in achieving symptom response at 72 hours


**Summary and Conclusions**

- Community-acquired pneumonia (CAP) remains a significant cause of morbidity and mortality in the U.S.; this entails high use of health care resources
- There is new appreciation of a wider array of CAP pathogens, notably viruses (some treatable)
- In community-acquired bacterial pneumonia (CABP) pathogen susceptibility is changing (e.g., Streptococcus pneumoniae, mycoplasma)
- Antibiotic selection driven by difficulty diagnosing pathogens, need to optimize coverage AND avoid toxicity
- Few new antibiotics over last 10 years for CABP; new antibiotics are on the horizon

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Thank you
Questions & Answers