Antimicrobial Stewardship Considerations in the Management of Lower Respiratory Tract Infection

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Medical Director, Department of Infection Control & Epidemiology
Objectives

At the conclusion of this program, participants should be able to:

1) Recognize the clinical importance of lower respiratory tract infections (LRTI)
2) Discuss a best practice approach to management of LRTI
3) Outline antimicrobial stewardship strategies for LRTI
Potential Conflicts of Interest

Dr Rupp reports potential conflicts of interest as follows:

- Research support in the form of contracts with UNMC: 3M, Contrafect, XBioTech, Magnolia, BARDA, NIH/DCRI
- Contract support for NE ICAP/ASP: CDC/NE HHS
- Consultant/Advisory Board: Magnolia, Citius, Teleflex, 3M
Respiratory Tract Infections

Upper Respiratory Tract Infections:
- 17,230,659,000 URI per year
- >90% viral, self-limited, **Antibiotics not indicated**
  (https://asap.nebraskamed.com/ambulatory-care/educational-materials-for-ambulatory-care/)

Lower Respiratory Tract Infections:
- 291,759,000 LRTI per year
- 2,236,700 deaths
- #1 cause of infection-related death

Deaths due to LRTI

Acute Bronchitis

**Definition:** Inflammation of the epithelial lining of the bronchi

**Incidence:** Very common – 3 million cases per year in the United States

**Etiology:** Usually viral

**Symptoms:** Cough, productive of sputum (often yellowish/gray/green; occasionally blood streaked), fatigue, mild fever or chills, chest discomfort. Usually follows cold or flu

**Diagnosis:** rule out pneumonia with CXR

**Course:** Self-limited, often lasts 2-3 weeks

**Treatment:** Supportive: rest, fluids. Symptomatic: cough suppressant, bronchodilators, mucolytics

**Prevention:** Quit smoking, flu vaccine
Chronic Bronchitis/ COPD

Should antibiotics be used to prevent AECB?

Macrolides reduce risk of AECB in pts prone to exacerbations, but is associated with increased resistance, QTc prolongation, and impaired hearing. Less benefit in active smokers. Not studied beyond 1 year.

When should antibiotics be used to treat acute exacerbation of chronic bronchitis?

• Exacerbations are usually triggered by viral infections
• Increased purulence & volume of sputum, increased dyspnea
• Differentiate viral from bacterial trigger with PCT
  • PCT <0.1 good marker for pts who will not benefit from Abx
  • PCT between 0.1-0.25 = unlikely to benefit
• Antibiotic choice: Doxycycline or Cefuroxime or Amox/clav or Azithromycin (avoid fluoroquinolones) x 5 days

Basics of Recognition and Management of Pneumonia
Community Acquired Pneumonia (CAP)

- CAP Clinical Significance
  - 1 million hospitalizations per year in United States
  - 8th leading cause of death
  - ~10 Billion dollars per year in direct cost

- Because CAP is common and can be life-threatening, guidelines have stressed early administration of potent antibiotics

- Clinical ambiguity and fear of missing life-saving therapeutic opportunities result in antibiotic misuse
Clinical Presentation of Pneumonia

- 10 million visits per year for cough, 5%-10% have pneumonia
- Cough, sputum production, dyspnea, chest pain, fever; non-respiratory complaints are common: fatigue, sweats, headache, myalgias, N/V/D/Abd pain.
- Increasing age & immunosuppression: less severe symptoms
Clues to Etiology of Pneumonia

- **Environmental Exposures:**
  - Contaminated aerosols/cooling towers: Legionella
  - Animal hides, wool, goat hair: anthrax
  - Bat/Bird Droppings, Caving: Histoplasmosis, Cryptococcus
  - Unpasteurized milk: Brucella
  - Water contaminated by rodent urine: Leptospirosis
  - Rodent droppings/urine: Hantavirus

- **Zoonotic Exposures:**
  - Cattle, Goats, Pigs: Brucella, Coxiella, Anthrax
  - Dogs/Cats: Pasteurella

- **Zoonotic (cont)**
  - Rodents in W US: Plague
  - Hunters/Rabbit exposure: Tularemia
  - Tickbites: Tularemia
  - Birds (parrots, pigeons, cockatoos, turkeys): Psittacosis
  - Goats/Cattle/Sheep/Domestic animals and secretions/birth products: Q fever

- **Travel:**
  - SW US: Coccidioidomycosis
  - Mississippi/Ohio valleys: Histoplasmosis, Blastomycosis
  - SE Asia: Melioidosis, Paragonimiasis (lung fluke)
  - Arabian Peninsula: MERS-coV
  - China: SARS
Clues to Etiology of Pneumonia

Underlying Diseases and Conditions:

- HIV:
  - Pneumococcus, Tb, Pneumocystis
- Influenza/Viral URI:
  - Staphylococcus
- IV Drug use:
  - Staphylococcus, R-sided endocarditis
- COPD:
  - H. influenzae, M. catarrhalis
- Splenectomy:
  - Pneumococcus, H flu, Neisseria
- Alcoholism/Dental work/Sz:
  - Aspiration/Anaerobes
- CF/Bronchiectasis:
  - Pseudomonas, Burkholderia, S. aureus
Physical Exam Findings

Respiratory Exam:
- Tachypnea, shallow breathing, cyanosis
- Increased fremitus with consolidation (decreased fremitus if effusion/empyema)
- Dullness to percussion, Crackles, Egophony (E to A), Whispered Pectoriloquy

Clinical Dx of Pneumonia is inaccurate:
- Sensitivity of 70%-90%, specificity of 40%-70%

Patients with clinical features suggesting Pneumonia should get a CXR
Why Examine and Culture Sputum?

- Optimize antibiotic selection in terms of activity against pathogen
- Limit consequences of antibiotic abuse in terms of cost, resistance, and adverse reactions
- Identify pathogens of epidemiologic significance
- There is diagnostic value of negative result. Negative culture rules out *Staphylococcus aureus*, MDR gram-negative bacilli.
Sputum Gram Stain
Bacterial Etiology of Community-Acquired Pneumonia

- **Pneumococcus**: 34%
- **H flu, M cat**: 15%
- **S aureus**: 6%
- **G(-) rods**: 8%
- **Anaerobes**: 8%
- **Legionella**: 7%
- **M pneumoniae**: 10%
- **Chlamydia pneumoniae**: 5%
- **Other**: 7%

Resp viruses ~1/3; alone or co-pathogen
Use of Procalcitonin to Guide Antibiotic Treatment for Pneumonia
Procalcitonin (PCT)

- PCT: Peptide produced by thyroid and converted into calcitonin to regulate calcium. Normally, very low levels found in blood.
- In LRTI, a variety of tissues produce PCT and levels quickly increase.
- PCT triggered by LPS as well as TNF, IL-1, IL-6 and is down regulated by IFN (induced by viral infection)

PCT vs Time

- PCT increases within 6-12 hours of infection
- $\frac{1}{2}$ life is 25-30 hours
- Sensitivity in LRTI: 94%; Specificity in LRTI: 88%
- Elevated in chronic renal failure and stage IV CHF
- Can be used to assist in diagnosis of bacterial LRTI and determination of duration of therapy
Odds of antibiotic initiation in 11 studies examining PCT in LRTI. OR of antibiotic initiation was 0.26 (95% CI 0.13-0.52).

Use of PCT in LRTI (Total Antibiotic Use)

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>AB use (days), mean (SD) PCT</th>
<th>AB use (days), mean (SD) Standard care</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Branch et al. (2015) [27]</td>
<td>3.67 (4.4)</td>
<td>4.00 (5.9)</td>
<td>-0.33 (-1.52 to 0.85)</td>
<td>11.06</td>
</tr>
<tr>
<td>Briel et al. (2008) [28]</td>
<td>6.20 (2.5)</td>
<td>7.10 (2.2)</td>
<td>-0.90 (-1.33 to -0.47)</td>
<td>12.31</td>
</tr>
<tr>
<td>Christ-Crain et al. (2006)</td>
<td>5.80 (5.3)</td>
<td>12.90 (6.5)</td>
<td>-7.10 (-8.44 to -5.76)</td>
<td>10.72</td>
</tr>
<tr>
<td>Corti et al. (2016) [32]</td>
<td>6.10 (7.4)</td>
<td>9.00 (7.4)</td>
<td>-2.90 (-5.55 to -0.25)</td>
<td>7.53</td>
</tr>
<tr>
<td>Schuetz et al. (2009) [35]</td>
<td>5.70 (5.2)</td>
<td>8.70 (3.7)</td>
<td>-3.00 (-3.48 to -2.52)</td>
<td>12.26</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkhardt et al. (2010) [29]</td>
<td>7.80 (2.8)</td>
<td>7.70 (3.3)</td>
<td>0.10 (-0.41 to 0.61)</td>
<td>12.23</td>
</tr>
<tr>
<td>Kristoffersen et al. (2009)</td>
<td>5.10 (4.1)</td>
<td>6.80 (4.7)</td>
<td>-1.70 (-2.90 to -0.50)</td>
<td>11.02</td>
</tr>
<tr>
<td>Long et al. (2011) [34]</td>
<td>4.75 (2.2)</td>
<td>7.00 (3.0)</td>
<td>-2.25 (-3.06 to -1.44)</td>
<td>11.80</td>
</tr>
<tr>
<td>Unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christ-Crain et al. (2004)</td>
<td>10.90 (3.6)</td>
<td>12.80 (5.5)</td>
<td>-1.90 (-3.07 to -0.73)</td>
<td>11.08</td>
</tr>
<tr>
<td>Stolz et al. (2007) [2]</td>
<td></td>
<td></td>
<td>(Excluded)</td>
<td></td>
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<tr>
<td>Verduri et al. (2015) [36]</td>
<td></td>
<td></td>
<td>(Excluded)</td>
<td></td>
</tr>
<tr>
<td>Overall (I² = 94.9%)</td>
<td></td>
<td></td>
<td>-2.15 (-3.30 to -0.99)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Difference in antibiotic use (Exposure: days prescribed vs Duration: days treated). Overall, pts in PCT cohort received weighted mean difference of 2.15 days less antibiotic use (95% CI 3.3 to 0.99).

Use of PCT in LRTI


### No difference in Length of Hospital Stay

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Length of HOS stay (days), mean (SD)</th>
<th>Length of HOS stay (days), mean (SD)</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>Standard care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christ-Crain et al. (2004) [30]</td>
<td>10.70 (8.9)</td>
<td>11.20 (10.6)</td>
<td>-0.50 (-2.97 to 1.97)</td>
<td>3.33</td>
</tr>
<tr>
<td>Christ-Crain et al. (2006) [31]</td>
<td>12.00 (9.1)</td>
<td>13.00 (9.0)</td>
<td>-1.00 (-3.04 to 1.04)</td>
<td>4.85</td>
</tr>
<tr>
<td>Corti et al. (2016) [32]</td>
<td>4.50 (3.0)</td>
<td>5.10 (4.4)</td>
<td>-0.60 (-1.96 to 0.76)</td>
<td>10.92</td>
</tr>
<tr>
<td>Kristoffersen et al. (2009) [33]</td>
<td>5.90 (4.7)</td>
<td>6.70 (4.7)</td>
<td>-0.80 (-2.07 to 0.47)</td>
<td>12.49</td>
</tr>
<tr>
<td>Schuetz et al. (2009) [35]</td>
<td>9.40 (5.9)</td>
<td>9.20 (5.9)</td>
<td>0.20 (-0.43 to 0.83)</td>
<td>50.93</td>
</tr>
<tr>
<td>Stolz et al. (2007) [2]</td>
<td>8.33 (10.4)</td>
<td>8.67 (10.4)</td>
<td>-0.33 (-3.15 to 2.49)</td>
<td>2.54</td>
</tr>
<tr>
<td>Verduzi et al. (2015) [36]</td>
<td>5.70 (4.2)</td>
<td>5.80 (3.7)</td>
<td>-0.10 (-1.26 to 1.06)</td>
<td>14.93</td>
</tr>
<tr>
<td>Branche et al. (2015) [27]</td>
<td>(Excluded)</td>
<td>(Excluded)</td>
<td></td>
<td></td>
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<tr>
<td>Overall (I² = 0.0%)</td>
<td></td>
<td></td>
<td>-0.15 (-0.60 to 0.30)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**WMD** -0.15

### No difference in Mortality

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Deaths, PCT (n/N)</th>
<th>Deaths, Standard care (n/N)</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branche et al. (2015) [27]</td>
<td>6/151</td>
<td>7/149</td>
<td>0.85 (0.29–2.46)</td>
<td>8.38</td>
</tr>
<tr>
<td>Briel et al. (2008) [28]</td>
<td>0/232</td>
<td>1/226</td>
<td>0.32 (0.01–7.93)</td>
<td>0.93</td>
</tr>
<tr>
<td>Christ-Crain et al. (2006) [31]</td>
<td>18/151</td>
<td>20/151</td>
<td>0.90 (0.50–1.63)</td>
<td>26.89</td>
</tr>
<tr>
<td>Corti et al. (2016) [32]</td>
<td>1/62</td>
<td>2/58</td>
<td>0.47 (0.04–5.02)</td>
<td>1.69</td>
</tr>
<tr>
<td>Kristoffersen et al. (2009) [33]</td>
<td>2/103</td>
<td>1/107</td>
<td>2.08 (0.19–22.57)</td>
<td>1.68</td>
</tr>
<tr>
<td>Schuetz et al. (2009) [35]</td>
<td>34/671</td>
<td>33/688</td>
<td>1.06 (0.66–1.69)</td>
<td>43.73</td>
</tr>
<tr>
<td>Stolz et al. (2007) [2]</td>
<td>5/102</td>
<td>9/106</td>
<td>0.58 (0.20–1.66)</td>
<td>8.50</td>
</tr>
<tr>
<td>Verduzi et al. (2015) [36]</td>
<td>3/88</td>
<td>2/90</td>
<td>1.53 (0.26–8.96)</td>
<td>3.06</td>
</tr>
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<td>Burkhardt et al. (2010) [29]</td>
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</tr>
<tr>
<td>Overall (I² = 0.0%)</td>
<td></td>
<td></td>
<td>0.94 (0.69–1.28)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**RR** 0.94
Patient level data on 6708 pts in 26 trials from 12 countries.

- Mortality significantly lower in PCT guided patients (9% vs 10%) (P=0.037)
- PCT guidance was associated with 2.4 day reduction in antibiotic exposure P<0.0001
- PCT guidance was associated with a significant reduction in antibiotic related side effects (16% vs 22%) P< 0.0001.

Proportion of patients on antibiotics & mean duration of antibiotic use (8.14 days vs 5.71 days)
Nebraska Medicine ASP

LRTI Initial Antibiotic Use Algorithm

- **PCT Value**
  - <0.1 μg/L: Strongly Discouraged
  - 0.1 - 0.24 μg/L: Discouraged
  - ≥ 0.25-0.5 μg/L: Encouraged
  - >0.5 μg/L: Strongly Encouraged

  - Consider alternative diagnosis
  - Repeat PCT in 6-12 hours if antibiotics not begun and no clinical improvement
  - If clinically unstable, immunosuppressed or high risk consider overruling (PSI Class IV-V, CURB>2, GOLD III or IV)

- **Antibiotic Use Recommendation**

https://www.nebraskamed.com/for-providers/asp/procalcitonin-pct-guidance
Duration of Antibiotic Treatment for Pneumonia
## Duration of Antibiotic Therapy

### What do the guidelines suggest?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Duration of Therapy</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDSA/ATS (2007)</td>
<td>5 days</td>
<td>Except in S aureus pneumonia with BSI or concurrent meningitis or endocarditis</td>
</tr>
<tr>
<td>ESCMID (2011)</td>
<td>≤ 8 days</td>
<td>PCT guidance suggested</td>
</tr>
<tr>
<td>NICE (2014)</td>
<td>5 days for low severity, 7-10 days for mod/high severity</td>
<td></td>
</tr>
<tr>
<td>IDSA/ATS: HAP/VAP (2016)</td>
<td>7 days</td>
<td>PCT guidance suggested</td>
</tr>
</tbody>
</table>

- “Cessation of therapy should be considered in patients with a favorable clinical response if PCT levels are ≤ 0.25 or have dropped > 80% from peak values.”
- “If PCT levels do not decreased adequately, treatment failure (empyema, resistance, inadequate abx) should be suspected.”

Antibiotic De-escalation in Treatment of Pneumonia
De-escalation of Antibiotic Therapy for Hospital Acquired Pneumonia


- 9 observational studies, 2128 patients with HAP/VAP
- De-escalation of empiric abx based on respiratory culture results
- Low quality to very low quality evidence (GRADE)
  - 30 day mortality: RR 0.73 (0.42-1.27)
  - ICU mortality: RR 0.74 (0.53-1.04)
  - Hospital mortality: RR 0.96 (0.74-1.24)
  - ICU stay: RR -3.04 (-7.57 to 1.49)
  - Hospital stay: RR -5.96 (-8.39 to -3.52)
Nasal screening for MRSA
19 studies, 21,790 patients
NPV (76%-99.4%) Ave: 93.5%
“Utilizing this test for ASP purposes can provide a valuable tool for reducing unwarranted anti-MRSA agents...” A cutoff of 7 days between nasal swab and infection onset seems most appropriate for use of this test for anti-MRSA agent de-escalation.”
“Healthcare-Associated” Pneumonia and Risk of Multi Drug-Resistant Pathogens
HCAP: 2005 IDSA/ATS pneumonia guideline – recommended abx for MDRO GNR and MRSA for broad group of patients:
  - Previous hospitalization for 2 days in past 3 months, residence in LTC, home infusion therapy, dialysis, wound care, family member with MDRO

- HCAP criteria is overly broad and does not identify pts with MDRO. At NMC only 5.9% of pts with HCAP criteria had MDRO (Gross et al. 2014)
- HCAP mortality due to underlying factors (age, co-morbidity) and not MDRO (Chalmers et al, CID 2011)
- No survival benefit to use of HCAP criteria and guideline concordant therapy
- Excess mortality in HCAP guideline compliant treatment (34% vs 20% (P=0.0042) (Kett et al. Lancet ID 2011)
Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

- No HCAP category
- Suspected HAP/VAP treatment driven by following risk factors for MDRO:
  - $\geq$ 5 days of hospitalization
  - Prior IV abx in past 90 d
  - Dialysis
  - Septic shock, ARDS
- Combination of Anti-pseudomonal beta-lactam + vanc (or linezolid); 2 GNR agents if resistance $> 10\%$
Barriers to Antimicrobial Stewardship in Management of LRTIs

Clinical and social barriers to antimicrobial stewardship in pulmonary medicine: A qualitative study

Jennifer K. Broom PhD a,b,*, Alex F. Broom PhD c, Emma R. Kirby PhD c, Alexandra F. Gibson PhD c, Jeffrey J. Post PhD d,e

AJIC 2017

- Diagnostic Ambiguity
  - Pneumonia vs Bronchitis vs non-infectious lower respiratory disease (CHF, PE, hemorrhage, aspiration pneumonitis, etc)
  - Bacterial infection vs viral
  - Colonization vs infection
- Under-appreciation of detrimental effects of inappropriate antibiotic use
  - Resistance, side effects, toxicity, CDI
- Lack of trust in guidelines
- Role models and hierarchy
Prevention of Pneumonia

SO YOU’VE BEEN BUSY.
But it’s not too late!

Get Flu Vaccination!

Quit Smoking
Final Words

1) Don’t treat URI with antibiotics
2) Don’t treat acute bronchitis with antibiotics
3) Carefully select patients with exacerbations of chronic bronchitis – based on signs/symptoms and procalcitonin level - for antibiotic treatment. Treat with Doxy or Amox/Clav; avoid fluoroquinolones
4) When encountering a pt with suspected pneumonia – be a good clinician and make a specific diagnosis
5) Use PCT to assist in determining which pts with pneumonia should be treated with antibiotics
6) Treat patients with pneumonia who are showing clinical response for 5-7 days (you can use PCT to assist with this decision)
7) Abandon the term HCAP and treat pts with HAP and VAP with antibiotic choice depending on risk of MDRO
Happy Trails
to You
Assessment Question 1

What is the typical duration of therapy for most cases of community-acquired pneumonia?

a) 3 to 5 days  
b) 5 to 7 days  
c) 7 to 10 days  
d) 10 to 14 days
Assessment Question 2

Procalcitonin can be used as a tool to support discontinuation of antimicrobial therapy for lower respiratory tract infections?

a) True
b) False