Lower Respiratory Infections (Pneumonia): Perspectives Amidst New Guidelines

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TAFP – August 2020
Dr. Winn has disclosed that he is on the speaker’s bureau for Allergan.
Learning Objectives

By the end of this educational activity, the learner should be better able to:

- Analyze the development and classification of pneumonia infection and evaluate the epidemiology and risk factors of community-acquired pneumonia.
- Identify etiological factors of community-acquired pneumonia, including pathogens most commonly associated with infection in adults and children and use established diagnostic criteria to appropriately identify and categorize community-acquired pneumonia.
- Outline the management of community-acquired pneumonia in adults and children, including the use of antibiotic therapy and appropriate site of care.
- Discuss prevention strategies, including vaccination, for community-acquired pneumonia.
Pneumonia: Pre-Antibiotic Era

- “Captain of the Men of Death”
  - Sir William Osler
- Mortality Rate High
  - Higher in face of Influenza pan/epidemics
- Role of Serum Therapy – Robert Austrian
  - Prelude to development of vaccine for *S. pneumoniae*

Along with Maxwell Finland, one of the 2 most important researchers into the biology of *Streptococcus pneumoniae* in the 20th century. Devised a multi-valent polysaccharide vaccine and then played a major role in the successful clinical trials which resulted in its licensure.
Alphabet Soup for Pneumonia: EIEIO!

- **CAP**: Community-acquired pneumonia
  - Outside of hospital or extended-care facility
- **HCAP**: Healthcare-associated pneumonia
  - Long-term care facility (NH), hemodialysis, outpatient chemo, wound care, etc.
- **HAP**: Hospital-acquired pneumonia
  - ≥ 48 h from admission
- **VAP**: Ventilator-associated pneumonia
  - ≥ 48 h from endotracheal intubation

*Semin Respir Crit Care Med.* Epub 2009 Feb 6, 3-9

*The alphabet soup of pneumonia: CAP, HAP, HCAP, NHAP, and VAP.*

*Anand N, Kollef MH*
Epidemiology

- 8th leading cause of death in US in 2007 (leading cause of death from infectious diseases worldwide, with an incidence of 0.3 to 0.5% in the adult population)

- 4-5 million cases per year in US – 60,000 deaths
  - 25% require hospitalization
  - Almost 916,000 cases annually in pts >65 yo

- Case fatality rate has not changed substantially since penicillin – (1st 24 hours)*

*Robert Austrian

www.cdc.gov/mmwr

www.cdc.gov/nchs/data/hestat
Pathophysiology


- Primary Acquisition is aspiration
  - Lesser risks – Inhalation, direct, hematogenous

- Role of Host and Pathogen – Increased virulence after antibiotic use

- Micro versus Macro-aspiration

- Location – RLL greatest risk due to anatomy


Microbiology

- Causative organism established in 60% CAP in research setting, 20% in clinical setting
- “Typical”:
  - S. pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Group A streptococci, Moraxella catarrhalis, anaerobes, and aerobic gram-negative bacteria
- “Atypical” – 20-28% CAP worldwide
  - Legionella spp, Mycoplasma pneumoniae, Chlamydophila (formerly Chlamydia) pneumoniae, and C. psittaci
  - Mainly distinguished from typical by not being detectable on Gram stain or cultivable on standard media

Community-acquired pneumonia requiring hospitalisation. Factors of importance for the short-and long-term prognosis.
Hedlund J
## Microbiology of CAP Among Hospitalized Patients

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
</table>
| **Outpatient**      | *Streptococcus pneumoniae*  
                      | *Mycoplasma pneumoniae*  
                      | *Haemophilus influenzae*  
                      | *Chlamydia pneumoniae*   
                      | Respiratory viruses     |
| **Inpatient (Ward)**| *S. pneumoniae*   
                      | *M. pneumoniae*   
                      | *H. influenzae*   
                      | *C. Pneumoniae*   
                      | *Legionella* species    
                      | Respiratory viruses     
                      | Aspiration              |
| **Inpatient (ICU)** | *S. pneumoniae*   
                      | *Legionella* spp.  
                      | *Staphylococcus aureus*|
                      | Gram-negative bacilli  |
Age-specific Rates of Hospital Admission by Pathogen

Typical vs. Atypical CAP

- N=24 +C. pneumoniae, N=13 Pneumococcal, N=8 Both

- CXR patterns
  - Bronchopneumonia: 88% C. pneumonia vs. 77% Pneumococcal, $P=0.67$
  - Lobar or air-space: 29% C. pneumonia vs. 54% Pneumococcal
## Comorbidities & Associated Pathogens

| Alcoholism                | ▪ *Strep pneumoniae*  
|                          | ▪ Oral anaerobes      
|                          | ▪ *Klebsiella pneumoniae*  
|                          | ▪ *Acinetobacter spp*  
|                          | ▪ *M. tuberculosis*    |
| COPD and/or Tobacco      | ▪ *Hemophilus influenzae*  
|                          | ▪ *Pseudomonas aeruginosa*  
|                          | ▪ *Legionella spp*     
|                          | ▪ *S. pneumoniae*      
|                          | ▪ *Moraxella catarrhalis*  
<p>|                          | ▪ <em>Chlamydophila pneumoniae</em>  |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration</td>
<td>▪ Gram-negative enteric pathogens</td>
</tr>
<tr>
<td></td>
<td>▪ Oral anaerobes</td>
</tr>
<tr>
<td>Lung Abscess</td>
<td>▪ <em>CA-MRSA</em></td>
</tr>
<tr>
<td></td>
<td>▪ Oral anaerobes</td>
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<tr>
<td></td>
<td>▪ Endemic fungi</td>
</tr>
<tr>
<td></td>
<td>▪ <em>M. tuberculosis</em></td>
</tr>
<tr>
<td></td>
<td>▪ Atypical mycobacteria</td>
</tr>
<tr>
<td>Structural lung disease (e.g. bronchiectasis)</td>
<td>▪ <em>P. aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td>▪ <em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td></td>
<td>▪ <em>S. aureus</em></td>
</tr>
<tr>
<td>Advanced HIV</td>
<td>▪ <em>Pneumocystis jirovecii</em></td>
</tr>
<tr>
<td></td>
<td>▪ <em>Cryptococcus</em></td>
</tr>
<tr>
<td></td>
<td>▪ <em>Histoplasma</em></td>
</tr>
<tr>
<td></td>
<td>▪ <em>Aspergillus</em></td>
</tr>
<tr>
<td></td>
<td>▪ <em>P. aeruginosa</em></td>
</tr>
</tbody>
</table>
# Zoonotic Exposures & Associated Pathogens

<table>
<thead>
<tr>
<th>Source of Exposure</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bat or bird droppings</td>
<td><em>Histoplasma capsulatum</em></td>
</tr>
<tr>
<td>Birds</td>
<td><em>Chlamydophila psittaci</em></td>
</tr>
<tr>
<td></td>
<td><em>Poultry: avian influenza</em></td>
</tr>
<tr>
<td>Rabbits</td>
<td><em>Francisella tularensis</em></td>
</tr>
<tr>
<td>Farm animals or parturient cats</td>
<td><em>Coxiella burnetti (Q fever)</em></td>
</tr>
</tbody>
</table>
## Exposures & Associated Pathogens

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotel or cruise ship</td>
<td><em>Legionella</em> spp</td>
</tr>
<tr>
<td>Travel or residence in SW US</td>
<td><em>Coccidioides</em> spp, <em>Hantavirus</em></td>
</tr>
<tr>
<td>Travel or residence in SE or E Asia</td>
<td><em>Burkholderia pseudomallei</em>, <em>Staph aureus</em>, <em>H.influenzae</em>, Avian influenza A (H5N1)</td>
</tr>
<tr>
<td>Influenza active in community</td>
<td><em>Influenza</em>, <em>S. pneumoniae</em>, <em>Staph aureus</em> (MRSA), <em>H. influenzae</em></td>
</tr>
<tr>
<td>Cough &gt;2 wks with whoop or posttussive vomiting</td>
<td><em>Bordetella pertussis</em></td>
</tr>
<tr>
<td>Clinical Features Associated with Specific Causes of CAP.</td>
<td></td>
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<tr>
<td>------------------------------------------------------------</td>
<td></td>
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<tr>
<td>Favoring typical bacterial or legionella pneumonia</td>
<td></td>
</tr>
<tr>
<td>Hyperacute presentation</td>
<td></td>
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<tr>
<td>Presentation with septic shock</td>
<td></td>
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<tr>
<td>Absence of upper respiratory symptoms</td>
<td></td>
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<tr>
<td>Initial upper respiratory illness followed by acute deterioration (suggesting viral infection with bacterial superinfection)</td>
<td></td>
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<tr>
<td>White-cell count, &gt;15,000 or ≤6000 cells per cubic millimeter with increased band forms</td>
<td></td>
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<tr>
<td>Dense segmental or lobar consolidation</td>
<td></td>
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<tr>
<td>Procalcitonin level, ≥0.25 μg per liter</td>
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<tr>
<td>Favoring atypical bacterial (mycoplasma or chlamydia) pneumonia</td>
<td></td>
</tr>
<tr>
<td>Absence of factors that favor typical bacterial pneumonia</td>
<td></td>
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<tr>
<td>Family cluster</td>
<td></td>
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<tr>
<td>Cough persisting &gt;5 days without acute deterioration</td>
<td></td>
</tr>
<tr>
<td>Absence of sputum production</td>
<td></td>
</tr>
<tr>
<td>Normal or minimally elevated white-cell count</td>
<td></td>
</tr>
<tr>
<td>Procalcitonin level, ≤0.1 μg per liter</td>
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<tr>
<td>Favoring nonbacterial (viral) pneumonia</td>
<td></td>
</tr>
<tr>
<td>Absence of factors that favor bacterial pneumonia</td>
<td></td>
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<tr>
<td>Exposure to sick contacts</td>
<td></td>
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<tr>
<td>Upper respiratory symptoms at time of presentation</td>
<td></td>
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<tr>
<td>Patchy pulmonary infiltrates</td>
<td></td>
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<tr>
<td>Normal or minimally elevated white-cell count</td>
<td></td>
</tr>
<tr>
<td>Procalcitonin level, ≤0.1 μg per liter</td>
<td></td>
</tr>
<tr>
<td>Favoring influenza pneumonia</td>
<td></td>
</tr>
<tr>
<td>Absence of factors that favor typical bacterial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Influenza active in the community</td>
<td></td>
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<tr>
<td>Sudden onset of flulike syndrome</td>
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<tr>
<td>Positive diagnostic test for influenza virus</td>
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</tbody>
</table>

MRSA
Modern-day CAP Pathogen

- 51 *Staphylococcus aureus* CAP cases in 19 states reported 2006-2007
- 79% MRSA
- Median age 16 yrs. (range <1 to 81)
- 47% antecedent viral illness
- 11 of 33 (33%) tested had lab-confirmed influenza
- 51% died a median of 4 days from symptom onset

Moral: Must consider MRSA coverage in severe CAP, esp. during flu season!

Diagnosis: Cultures

- **Pre-tx Blood Cultures**
  - Yield 5-15%
  - Stronger indication for severe CAP
  - Host factors: cirrhosis, asplenia, complement deficiencies, leukopenia

- **Pre-tx expectorated sputum GS & Cx**
  - Yield can be variable — Rapid etiological tests, such as sputum Gram stain and urinary antigen tests, are useful for targeting initial pathogen-directed therapy- *Int J Antimicrob Agents* 2008
  - Depends on multiple factors: specimen collection, transport, speed of processing, use of cytologic criteria — Mayo Clinic Criteria – John Washington
  - Predominant morphotype seen in only 14% of 1669 hospitalized CAP pts (Garcia-Vasquez, *Arch Intern Med* 2004)

- **Pre-tx endotracheal aspirate GS & Cx**

- **Pleural effusions >5 cm on lateral upright CXR**
How to Obtain a Nasopharyngeal Swab
Diagnosis – Bronchoscopy – Quantitative Cultures

- Protected Specimen Brush
  - $10^4$ CFU (Colony forming units)/ml
- Protected BAL (not washings)
  - $10^3$ CFU/ml
- Percentage of granulocytes with ingested bacteria
- Value of Negative stain and culture to R/O pneumonia
Diagnosis: Other Testing

- **Urinary antigen tests**
  - *S. pneumoniae* & *L. pneumophila* serogroup 1
  - 50-80% sensitive, >90% specific in adults
  - Pros: Rapid (15 min), simple, can detect *Pneumococcus* after abx started
  - Cons: Cost, no susceptibility data, not helpful in patients with recent CAP (prior 3 months)
Diagnosis: Other Testing

- Acute-phase serologies
  - *C. pneumoniae*, Mycoplasma, *Legionella* spp
  - Not practical given slow turnaround & single acute-phase result unreliable

- Influenza testing
  - Hospitalized patients: Severe respiratory illness (T> 37.8°C with SOB, hypoxia, or radiographic evidence of pneumonia) *without* other explanation and suggestive of infectious etiology should get screened during season
  - NP swab or nasal wash/aspirate
  - Rapid flu test (15 min)
    - Distinguishes A vs B
    - Sensitivity 50-70%; specificity >90%
  - Respiratory virus DFA & culture – reflex subtyping for A
  - Respiratory viral PCR panel – reflex subtyping for A
  - Influenza A PCR panel
CAP Guidelines – Rationale

- In the areas of pulmonary, infectious diseases, and critical care medicine, no guideline has greater validity and acceptance than that for management of community-acquired pneumonia (CAP).
- These guidelines have been incorporated into quality metrics, pay-for-performance, and public reporting of physician and hospital care.
- Because pneumonia is the leading cause of adult admissions in the United States, the leading cause of infectious deaths, and in the differential of the most frequent symptom complexes in outpatient primary care, this attention to CAP guidelines is neither surprising nor inappropriate.
The rationale for CAP guidelines has evolved over the last few decades. Significant variability in antibiotic prescription for CAP without differences in outcome was a primary driver of the initial efforts to derive guidelines. Almost every new antibiotic received a US Food and Drug Administration (FDA) indication for CAP, resulting in a plethora of individual antibiotics among which to choose. The cost/benefit relationship of these new more expensive agents compared with each other and to generic antibiotics was unclear. Initial CAP guidelines attempted to address these issues through the opinion of experts in the field and were sponsored by professional societies. In the United States, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) led these efforts.
Despite the basis of expert opinion only and a lack of randomized controlled trials specifically comparing guideline-recommended therapy to usual care, subsequent studies consistently demonstrated improved outcomes as a greater proportion of CAP patients were managed according to ATS/IDSA CAP guidelines.

The Centers for Medicare and Medicaid Services recognized the benefit of compliance with these guidelines by incorporating antibiotic choices consistent with ATS/IDSA guidelines as a major quality metric for public reporting.
The guidelines have expanded to address other issues, including appropriate diagnostic testing and the use of adjunctive therapies.

New challenges for antibiotic management have also arisen, including the role of *Legionella* and community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), and the emergence of CAP cases with other resistant pathogens typically associated with nosocomial infections and temporarily designated as health care-associated pneumonia (HCAP).
Despite these theoretic benefits of macrolides, the major driving force for the IDSA/ATS guideline recommendation for beta-lactam/macrolide combination therapy was a consistent survival benefit for combination therapy in large public and administrative databases. Theoretic benefits of macrolides were only explored to explain the observed effect.

In contrast, proponents of beta-lactam monotherapy base their recommendation on the overwhelming dominance of pneumococcus (in addition of other Streptococci) as the cause of CAP. Atypical pathogen coverage is then reserved for patients with specific risk factors or failure of prior beta-lactam therapy.

Routine macrolide combination therapy is not warranted, outside of intensive care unit (ICU) admissions, based on drug toxicity and the potential for development of resistance.
Many other countries and regions have also developed CAP guidelines, including published guidelines from Great Britain, Spain, the Netherlands, Sweden, Japan, and China.

Most guidelines roughly parallel those of the IDSA/ATS or northern Europe.

Although differences are relatively minimal, these local and regional differences are actual internally consistent with a major emphasis in most guidelines for local adaptation of recommendations.
The major difference between the IDSA/ATS CAP guidelines and those of northern European countries is the need for macrolide combination with beta-lactams for hospitalized, non-ICU patients.

Several justifications for macrolide combination exist. The primary is coverage of atypical bacterial pathogens (Mycoplasma, Chlamydophila, and Legionella). Because detection of these pathogens was difficult, empirical coverage was recommended.

However, rates of Mycoplasma and Chlamydophila vary by seasons and can occur in occult epidemics.

Other potential benefits include an anti-inflammatory effect on host immune response as well as suppression of the pore-forming exotoxin pneumolysin, a major virulence factor for Streptococcus pneumoniae.
Three informative major studies have been published since the last guidelines. First, the large multicenter Centers for Disease Control and Prevention-sponsored Epidemiology of Pneumonia In the Community (EPIC) study found that the proportion of adults with detection of an atypical bacterial pathogen was 3.7%.

In contrast, pneumococcal detection occurred in only 5.1%, despite extensive diagnostic testing. Additional cases of pneumococcal pneumonia were subsequently found with research-only diagnostic tests but still remain less than 15% of all detections. These dramatically lower detection rates for the pneumococcus compared with previous epidemiologic studies likely represent the effect of near universal pediatric conjugate pneumococcal vaccination and increased smoking cessation efforts.
A large multicenter cluster-randomized trial in the Netherlands appeared to support beta-lactam monotherapy as equivalent to both IDSA/ATS-recommended treatment regimens. However, many aspects of the trial design call into question this conclusion. Because of a public health orientation, the chosen primary endpoint was 90-day mortality. This endpoint is compromised by a greater effect of underlying diseases, such as metastatic cancer, and intercurrent illnesses, especially cardiovascular events. The latter may be related to CAP, but the relationship to type of antibiotic treatment is very unclear. A more pertinent endpoint is need for alteration of the antibiotic regimen, which was 8.8% for beta-lactam monotherapy compared with 6.1% for combination and 3.7% for fluoroquinolone monotherapy.

The study was also compromised by a large proportion of patients who crossed over treatment from that assigned.

Differences in health care systems are relevant: the hospital length of stay (LOS) for the Netherlands is greater than 6 days in contrast to approximately 3 days in the United States.

This longer observation time allows recognition of failing therapy before discharge, thus avoiding readmission, which is now a major issue for public reporting of the quality of CAP management in the United States.
A head-to-head randomized controlled trial of macrolide/beta-lactam combination with monotherapy with the identical beta-lactam for non-ICU hospitalized CAP patients has finally been published*.

Designed similar to antibiotic FDA-registration trials, the primary endpoint was the more clinically relevant time to clinical stability, a measurement associated with safe discharge and low risk of readmission.

The difference in proportions achieving clinical stability by day 7 was 7.6% (95% confidence interval of the difference 0.8%–16%).

In addition, serious adverse events of death and ICU transfer only occurred in monotherapy patients, and readmission rates were higher in the monotherapy group.

Based on this study, if beta-lactam monotherapy was a new antibiotic, the probability of FDA approval would be very low.

A synthesis of these data is that a large proportion of CAP patients can be treated successfully with beta-lactam monotherapy but are more likely to fail without careful attention and potentially longer hospitalization.

If the role of guidelines is to indicate the best treatment of most CAP patients, especially for primary care physicians and hospitalists, combination therapy clearly gives more consistent and lower risk.

An analysis of risk benefit confirms that macrolides are not benign but that the mortality cost of not including macrolides with beta-lactams outweighs this risk.
To Admit or Not?
Pneumonia Severity & Deciding Site of Care

- Using objective criteria to risk stratify & assist in decision re outpatient vs inpatient management
- PSI
- CURB-65
- Caveats
  - Other reasons to admit apart from risk of death
  - Not validated for ward vs ICU
  - Labs/vitals dynamic
<table>
<thead>
<tr>
<th>Common Causes</th>
<th>Less Common Causes</th>
<th>Uncommon Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae,</em></td>
<td><em>Pseudomonas aeruginosa</em> or other gram-negative rods, <em>Pseudomonas jirovecii,</em></td>
<td><em>Mycobacterium tuberculosis,</em> nontuberculous mycobacteria, <em>nocardia species,</em></td>
</tr>
<tr>
<td><em>Haemophilus influenzae,</em></td>
<td><em>Moraxella catarrhalis,</em> mixed microaerophilic and anaerobic oral flora</td>
<td><em>legionella species,</em> <em>Mycoblastes pneumoniae,</em> <em>Chlamydia pneumoniae</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus,</em></td>
<td></td>
<td><em>Chlamydia psittaci,</em> <em>Coxiella burnetii,</em> <em>Histoplasma capsulatum,</em> <em>coccidioides</em></td>
</tr>
<tr>
<td>influenza virus, other respiratory viruses†</td>
<td></td>
<td>species,* <em>Blastomyces dermatitidis,</em> <em>cryptococcus</em> and <em>aspergillus</em> species</td>
</tr>
<tr>
<td>Noninfectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema, lung cancer, acute respiratory</td>
<td>Pulmonary infarction</td>
<td>Cryptogenic organizing pneumonia, eosinophilic pneumonia, acute interstitial</td>
</tr>
<tr>
<td>distress syndrome</td>
<td></td>
<td>pneumonia, sarcoidosis, vasculitis (granulomatosis with polyangiitis),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pulmonary alveolar proteinosis, drug toxicity, radiation pneumonitis</td>
</tr>
</tbody>
</table>

* Causes of pneumonia vary according to the patient population, host immune status, and geographic region. No cause is determined in about half of patients with CAP despite intense investigation. Normal flora, especially streptococci from the upper airways, may be responsible for many of these cases.
† Routine use of the polymerase-chain-reaction (PCR) assay has substantially increased the detection of these agents, which include para-influenza virus, respiratory syncytial virus, adenovirus, coronavirus, human metapneumovirus, and rhinovirus.
‡ The frequency of this organism in causing CAP is uncertain because serologic techniques have been unreliable. Currently available PCR assays may provide reliable information in the future.
Pneumonia Severity Index

PORT Study


![Decision Tree Diagram](image_url)

**Characteristics**

**Demographic factors**
- Age
  - Men: Age (in yr)
  - Women: Age (in yr) + 10
- Nursing home resident: +10

**Coexisting illnesses**
- Neoplastic disease: +30
- Liver disease: +20
- Congestive heart failure: +10
- Cerebrovascular disease: +10
- Renal disease: +10

**Findings on physical examination**
- Altered mental status: +20
- Respiratory rate >30/min: +20
- Systolic blood pressure <90 mm Hg: +20
- Temperature <35°C or >40°C: +15
- Pulse >125 beats/min: +10

**Laboratory and radiographic findings**
- Arterial pH <7.35: +30
- Blood urea nitrogen >30 mg/dl (11 mmol/liter): +20
- Sodium <135 mmol/liter: +20
- Glucose >250 mg/dl (14 mmol/liter): +10
- Hematocrit <30%: +10
- Partial pressure of arterial oxygen <60 mm Hg or oxygen saturation <90%: +10
- Pleural effusion: +10

**Stratification of Risk Score**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Risk Class</th>
<th>Score</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>I</td>
<td>Based on algorithm</td>
<td>0.1%</td>
</tr>
<tr>
<td>Low</td>
<td>II</td>
<td>&gt;70</td>
<td>0.0%</td>
</tr>
<tr>
<td>Low</td>
<td>III</td>
<td>71–90</td>
<td>0.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>IV</td>
<td>91–130</td>
<td>9.3%</td>
</tr>
<tr>
<td>High</td>
<td>V</td>
<td>&gt;130</td>
<td>27.0%</td>
</tr>
</tbody>
</table>
Criteria for Severe CAP

**Minor criteria**
- Respiratory rate ≥30 breaths/min
- PaO2/FiO2 ratio ≥ 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN ≥20 mg/dL)
- Leukopenia (WBC <4000 cells/mm³)
- Thrombocytopenia (platelets <100,000 cells/mm³)
- Hypothermia (core T <36°C)
- Hypotension requiring aggressive fluid resuscitation

**Major criteria**
- Invasive mechanical ventilation
- Septic shock with the need for vasopressors
Prognostic Signs and Symptoms

- Negative
  - Multilobar disease
  - Very High WBC count
  - Very High Percentage of Immature granulocytes
  - Shock (Use of Pressors)
  - Multiorgan system failure

Prognostic factors for community-acquired pneumonia in middle-aged and elderly patients treated with integrated medicine.

Independent predictive risk factors correlated with adverse outcomes in elderly patients were higher respiration rate, CRP > or = four times the mean or median for the patient's center, cost of hospitalization >11,323 RMB and PSI >11, plus anemia, gasping, confusion and moist rales; those in middle-aged patients were higher Neu%, BUN > or = mean or median, loss of appetite, anemia, confusion, being retired or unemployed and lower educational level. Gram-negative bacterial infection and time to clinical stability >9 days were protective factors.
Pneumonia Treatment Considerations

- Outpatient – Oral Therapy
- Inpatient – Parenteral Therapy
Outpatient Empiric CAP Abx

- Healthy; no abx x past 3 months
  - Macrolide, i.e.; azithromycin, clarithromycin
  - 2nd choice: Doxycycline

- Comorbidities; Abx x past 3 months (use alternative abx)(HCAP?)
  - Respiratory fluoroquinolone: Moxifloxacin, levofloxacin 750 mg, gemifloxacin
  - Beta-lactam + macrolide

- Regions with >25% high-level macrolide-resistant S. pneumo, consider alternative agents

2007 IDSA/ATS Guidelines for CAP in Adults.
Community-acquired pneumonia (CAP) accounts for 78% of deaths from infectious diseases in the United States, but outcomes continue to be highly variable even on a county level.

The preponderance of evidence favors use of b-lactam/macrolide combination therapy over b-lactam monotherapy for hospitalized, non-intensive care unit patients.

The decreasing incidence of pneumococcal pneumonia and greater viral detections in CAP due to public health efforts, especially pneumococcal conjugate vaccine, will impact future guideline management recommendations.

The health care associated pneumonia definition overestimates the small subgroup of CAP patients with pathogens resistant to the usual antibiotic regimens; new risk stratification is needed for individual pathogens, such as methicillin-resistant Staphylococcus aureus.

### Table 3. Empirical Treatment of CAP.

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong>&lt;sup&gt;+&lt;/sup&gt;</td>
<td>For syndromes suggesting typical bacterial pneumonia: amoxicillin–clavulanate with the addition of azithromycin if legionella species are a consideration; levofoxacin or moxifloxacin may be used instead.</td>
</tr>
<tr>
<td></td>
<td>For syndromes suggesting influenza pneumonia: oseltamivir with observation for secondary bacterial infection.</td>
</tr>
<tr>
<td></td>
<td>For syndromes suggesting viral pneumonia other than influenza: symptomatic therapy.</td>
</tr>
<tr>
<td></td>
<td>For syndromes suggesting mycoplasma or chlamydia pneumonia: azithromycin or doxycycline.</td>
</tr>
<tr>
<td><strong>Inpatient</strong>&lt;sup&gt;↓&lt;/sup&gt;</td>
<td>For initial empirical therapy: a beta-lactam (cefixime, cefotaxime, or ceftriaxone) plus azithromycin; levofoxacin or moxifloxacin may be used instead.</td>
</tr>
<tr>
<td></td>
<td>If influenza is likely: oseltamivir.</td>
</tr>
<tr>
<td></td>
<td>If influenza is complicated by secondary bacterial pneumonia: ceftriaxone or cefotaxime plus either vancomycin or linezolid&lt;sup&gt;↓&lt;/sup&gt; in addition to oseltamivir.</td>
</tr>
<tr>
<td></td>
<td>If <em>Staphylococcus aureus</em> is likely: vancomycin or linezolid in addition to the antibacterial regimen.</td>
</tr>
<tr>
<td></td>
<td>If <em>Pseudomonas</em> pneumonia is likely: antipseudomonal beta-lactam (piperacillin–tazobactam, cefepime, meropenem, or imipenem–cilastatin) plus azithromycin.</td>
</tr>
</tbody>
</table>

<sup>+</sup> The decision to treat pneumonia on an outpatient basis should be made after assessing the need for hospitalization and only if follow-up contact is planned. The use of quinolones is typically reserved for outpatients with substantial coexisting illnesses or recent use of antibiotics from another class.

<sup>↓</sup> Patients who are hospitalized for pneumonia are sufficiently likely to have a bacterial infection that antibacterial agents are nearly always prescribed unless an alternative diagnosis is strongly suspected. In every hospitalized patient, all reasonable efforts should be made to determine the causative organism, and antimicrobial therapy should be directed toward identified organisms.

<sup>†</sup> In patients who are severely ill, intravenous zanamivir can be obtained after approval of an emergency investigational new drug application.

<sup>‡</sup> These regimens target the most likely causes of bacterial pneumonia secondary to influenza pneumonia, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Str. pyogenes*, and *Staph. aureus*. Ceftriaxone may be effective against these bacterial pathogens, including methicillin-resistant *Staph. aureus* (MRSA), but it is not yet approved by the Food and Drug Administration for MRSA pneumonia.

<sup>¶</sup> A second antipseudomonal drug (ciprofloxacin or an aminoglycoside) can be added in patients with severe CAP in whom *P. aeruginosa* is likely, because susceptibility is difficult to predict. Therapy can be narrowed to one agent with activity against gram-negative bacilli once susceptibility results are available.
<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Recommended</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient: previously healthy</td>
<td>Macrolide</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Outpatient: underlying disease/previous treatment</td>
<td>Fluoroquinolone</td>
<td>Beta-lactam combined with macrolide or doxycycline</td>
</tr>
<tr>
<td>Non-ICU inpatient</td>
<td>Beta-lactam combined with macrolide or fluoroquinolone monotherapy</td>
<td>Beta-lactam combined with doxycycline</td>
</tr>
<tr>
<td>ICU patient</td>
<td>Beta-lactam combined with macrolide or beta-lactam combined with fluoroquinolone</td>
<td>Add linezolid or vancomycin for suspected MRSA Change to anti-pseudomononal beta-lactam and quinolone if suspect pseudomonas</td>
</tr>
</tbody>
</table>
Only one antibiotic with an entirely new mechanism of action is on the FDA fast track for approval for CAP.

Lefamulin, the first of the pleuromutilin class of antibiotics, appears to have activity equivalent to moxifloxacin, arguably the best fluoroquinolone for CAP, while having a spectrum that includes MRSA.

Drawbacks include limited gram-negative coverage, even for the occasional CAP pathogen.

The entirely different mechanism of action makes salvage therapy for prior failures for either fluoroquinolones or beta-lactam/macrolide attractive.
Minimizing Fluoroquinolone Use

- Lost in the debate regarding the need for macrolides are the excellent results with respiratory fluoroquinolones, which have CAP outcomes equivalent or better than beta-lactam/macrolide combination therapy.

- However, a major emphasis of current antibiotic stewardship efforts is to minimize use of quinolones when other legitimate alternatives exist.

- This pressure to minimize quinolones is based on emerging data on toxicities and the fact that quinolones remain one of the few orally active agents for serious gram-negative infections.
Biomarkers for Prognosis

- Utility of two biomarkers for directing care among patients with non-severe community-acquired pneumonia.
- CURB score and Procalcitonin
- Correlation high with increasing severity of pneumonia with the height of the procalcitonin

Biomarkers for Prognosis

A new diagnostic and prognostic approach relies on evaluation of biomarkers as an expression of the host's inflammatory response against the microorganism.

- Analysis of systemic biomarkers in addition to clinical scores [Pneumonia Severity Index (PSI) or CURB-65 (confusion, urea, respiratory, blood pressure, >65 years)/CRB-65 (confusion, respiratory, blood pressure)] has been shown to improve 30-day mortality prediction and absence of severe complications.

- Pro-ADM (pro-adrenomedullin) is probably the biomarker that correlates most strongly with mortality prediction.

_Biomarkers and community-acquired pneumonia: tailoring management with biological data._
_Torres A, Ramirez P, Montull B, Menéndez R._
Procalcitonin

- Trials for Superiority in lowering antibiotic use and
- Non-inferiority for mortality
- 630 patients*
- 28- and 60-day mortality unaffected
- Duration of antibiotic therapy shortened significantly

Procalcitonin – Prognostically

- Gibot et al* – 1671 patients with documented CAP
- Prognostic value of PCT compared to CURB score, WBC and CRP
- Elevated PCT was significantly related to severity of CAP compared to PSI
- Continued elevations correlated with increasing mortality risks from day 1-3

NEJM, 2004;350:451
Procalcitonin – Bottom Line

- May be useful to decrease antibiotic exposure (cost?)
- Non-inferior with regard to mortality
- Appears useful for assessing on-going severity
- PCT >0.36 ug/ml sensitivity of 85%, specificity of 42%, NPV 98% in predicting positive Blood cultures
- PCT <0.5 ug/ml NPV of predicting viral/atypical versus bacterial CAP

Menendez, CHEST 2011;11:1-28
Duration

- In general, (5 OP) 7-8 days with last 2 being afebrile
- No confounding variables
- Extrapolated from Kollef – VAP data*

*Short- vs. Long-Duration Antibiotic Regimens for Ventilator-Associated Pneumonia: A Systematic Review and Meta-analysis. Four randomized controlled trials (RCTs) comparing short (7-8 days) with long (10-15 days) regimens were identified. Primary outcomes included mortality, antibiotic-free days, and clinical and microbiologic relapses. Secondary outcomes included mechanical ventilation-free days, duration of mechanical ventilation, and length of ICU stay. Short-course treatment of VAP was associated with more antibiotic-free days. No difference was found regarding mortality and relapses; however, a strong trend for fewer relapses was observed in favor of the long-course treatment.
Influenza Pneumonia
Some things to keep in mind…

- Antiviral treatment within 48 hrs.
  - Reduce likelihood of lower tract complications & antibacterial use in outpatients
  - Impact on hospitalized pts less clear

- Possible exceptions to <48 h rule:
  - Immunocompromised patients
  - To reduce viral shedding for infection control in hospitalized patients
Influenza Pneumonia

Some things to keep in mind…

- Influenza B
  - Oseltamivir – 75 mg PO BID x 5 days
  - Zanamivir – 2 INH BID x 5 days

- Influenza A
  - H3N2 – General seasonal
    - Resistant to adamantane antivirals
  - H1N1 – General seasonal
    - High rate of oseltamivir resistance in 2008-2009
    - Still susceptible to zanamivir
  - Novel H1N1 (Swine flu)
    - Sensitive to neuraminidase inhibitors
    - Resistant to adamantanes
Drug-resistant *Strep pneumoniae* β-lactam Resistance

- **Risk factors**
  - Age >65 yrs.
  - β-lactam x previous 3 months
  - Medical comorbidities
  - Exposure to child in day care

- Current levels of β-lactam resistance do not generally result in treatment failure with amoxicillin, ceftriaxone or cefotaxime
  - As opposed to macrolide or fluoroquinolone resistance

- Clinically relevant threshold – MIC 4?
Follow-up Response

Expected Improvement?

- Clinical improvement w/ effective abx: 48-72 hrs.
- Fever can last 2-5 days with Pneumococcus, longer with other etiologies, esp. Staph aureus
- CXR clearing
  - If healthy & <50 yo, 60% have clear CXR x 4 wks
  - If older, COPD, bacteremic, alcoholic, etc. only 25% with clear CXR x 4 wks
- Switch from IV to PO
  - Hemodynamically stable, improving clinically
  - Afebrile for 24-48 hours
  - Able to ingest meds with working GI tract
Inadequate Response to Therapy
What to Consider

- Consider *S. aureus*, virus, resistant organism, TB, endemic fungi, *Pneumocystis*
- More unusual pathogens, atypical mycobacteria, higher bacteria (Nocardia, actinomycetes), fungi
- Noninfectious illness:
  - Lung neoplasms with bronchial obstruction
  - Lymphoma
  - Systemic autoimmune disorders
  - PE w/ infarct, pulm edema, ARDS
- Consider other testing:
  - Lower tract sampling (bronch)
  - CT chest
  - PE work-up?
  - Serologic testing
  - Open lung biopsy
<table>
<thead>
<tr>
<th>All drug-resistant pathogens</th>
<th>1. Prior broad-spectrum antibiotic therapy</th>
<th>2. Recent hospitalization</th>
<th>3. Immunocompromising drugs or conditions</th>
<th>4. Prior colonization/infection with drug-resistant pathogen</th>
<th>5. Nursing home patients unable to perform activities of daily living, gastrostomy, tracheostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA-MRSA</td>
<td>Hemoptysis</td>
<td>Hemodialysis</td>
<td>Structural lung disease</td>
<td>Alcoholism</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>Influenza season</td>
<td>Congestive heart failure</td>
<td>Severe chronic obstructive pulmonary disease</td>
<td>Cigarette smoking</td>
<td>Gastric acid suppression</td>
</tr>
<tr>
<td></td>
<td>Neutropenia from infection</td>
<td></td>
<td>Bronchiectasis</td>
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Table 2
Risk factors for pathogens resistant to usual community-acquired pneumonia treatment
Increasing Evidence of Viral Cause in Adult Community-Acquired Pneumonia

- The EPIC study found that viral detections were significantly more common in adult CAP than bacterial.
- A large proportion (65%) of the EPIC patients without etiologic detections had procalcitonin (PCT) levels in the range (≤0.25 ng/dL) seen with viral infection and safely managed without antibiotics.
- The combination of more extensive use of respiratory viral panels and increased availability of PCT offers the opportunity to not only diagnose viral CAP but also, more importantly, avoid prolonged courses of antibiotics. Several meta-analyses demonstrate the safety of avoiding antibiotics in patients with persistently low PCT levels.
- Persistently low PCT, especially in the setting of a positive respiratory panel, can be used to stop antibiotics and shift to symptomatic care.
- The only viral pneumonia with a legitimate treatment option currently is influenza.
One of the other major findings of the EPIC study is that routine diagnostic testing for CAP cause is restricted and incomplete: 64% of adults had no pathogen detected.

Bacteremia rates have fallen dramatically, partially because of greater emphasis on rapid delivery of antibiotics. Even a single dose of antibiotic may be enough to make blood and respiratory tract cultures negative.

Molecular diagnostics offer an alternative to traditional culture-based methods. They are already the standard for respiratory viral diagnosis.

Greatest limitation is the inability to detect pathogens directly from blood, and therefore pathogens are susceptible to some of the same limitations as sputum cultures.

Most molecular tests will only detect the presence of a pathogen and offer no data on antibiotic susceptibility, similar to what is currently available with urinary antigen detection of S. pneumoniae or Legionella pneumophila.

No study yet has compared management based on these rapid diagnostic tests to standard limited testing and empirical antibiotic therapy.
Management of Severe Community-Acquired Pneumonia

- No prospective randomized controlled trial has been performed specifically on antibiotic treatment of severe CAP patients.
- The definition of severe CAP is variable but, specifically, mechanically ventilated and vasopressor-dependent CAP patients are routinely excluded from antibiotic trials.
- Therefore, treatment regimens are based on case series or cohort studies, often retrospective.
- Most guidelines recommend use of combination therapy with a beta-lactam and either a macrolide or a fluoroquinolone.
- Support for the former includes retrospective studies of bacteremic cases, although not all studies find a survival advantage for combination therapy.
Many studies also demonstrate a slight but clearly higher incidence of less common CAP pathogens in severe CAP, mainly *S aureus* but also including those bacteria often associated with hospital-acquired infections.

The tendency to use broad-spectrum treatment is somewhat understandable. However, the current level of evidence, although retrospective, suggests worse outcome with broad spectrum therapy.

These contrasting findings result in an additional 2 different challenges to CAP guideline development: definition of patients who do benefit from broad-spectrum therapy and, alternatively, need for adjunctive therapy in severe CAP patients on appropriate antibiotics.
Antibiotic Stewardship Strategies for CAP*

- ASP Strategies are appropriate in order to maintain or improve patient outcomes.
- In this regard, antibiotic de-escalation, duration of antibiotic treatment, adherence to CAP guidelines recommendations about empirical treatment, and switching from intravenous to oral antibiotic therapy may each be relevant in this context.
- Antimicrobial stewardship strategies, such as prospective audit with intervention and feedback, clinical pathways, and dedicated multidisciplinary teams, that have included some of these elements have demonstrated improvements in antimicrobial use for CAP without negatively affecting clinical outcomes.

Prevention

- Immunization
  - Pneumovax (polysaccharide)
  - Prevnar (conjugated vaccine with protein)
  - Influenza (annually)
- Special Circumstances
  - Immunocompromised/Asplenia
    - Both *S. pneumoniae* vaccines
    - Consider Menactra, Hib
Pneumonia Vaccines

- Pneumococcal polysaccharide vaccine – the latest version is known as Pneumovax 23 – Is the first pneumococcal vaccine
  - The first vaccine derived from a capsular polysaccharide, and an important landmark in medical history.
  - The polysaccharide antigens were used to induce type-specific antibodies that enhanced opsonization, phagocytosis, and killing of pneumococci by phagocytic cells.
  - PNEUMOVAX 23 is approved for use in persons 50 years of age or older and persons aged >2 years who are at increased risk for pneumococcal disease.
Pneumonia Vaccines

- Prevnar 13 is a vaccine approved for adults 50 years of age and older for the prevention of pneumococcal pneumonia and invasive disease caused by 13 Streptococcus pneumoniae strains (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

- For children 6 weeks through 17 years of age, Prevnar 13 is approved for the prevention of invasive disease caused by the 13 vaccine strains, and for children 6 weeks through 5 years for the prevention of otitis media caused by 7 of the 13 strains.

- Prevnar 13 is not 100% effective and will only help protect against the 13 strains included in the vaccine.

- Effectiveness when given less than 5 years after a pneumococcal polysaccharide vaccine is not known.
Pneumonia Vaccine

- The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) has recommended that immunocompromised adults receive a second pneumococcal vaccine.

- The recommendation for immunization with the 13-valent pneumococcal conjugate vaccine (Prevnar 13, PCV13) in addition to the 23-serotype polysaccharide vaccine (Pneumovax 23, PPSV23) was made at the ACIP’s meeting on June 20, 2012, in Atlanta.

- Adults aged 19 and older with immunocompromising conditions who have not previously received PCV13 or PPSV23 should receive a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later. Adults aged 19 and older with immunocompromising conditions who have previously received at least one dose of PPSV23 should receive a single dose of PCV13 no sooner than 1 year after the last PPSV23 dose. If patients require another PPSV23 dose, it should be administered no sooner than 8 weeks after PCV13 and 5 years after the last PPSV23 dose.
Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

- Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications. Vaccination optimally should occur before onset of influenza activity in the community.

- Antibody levels induced by vaccine decline postvaccination. Although a 2008 literature review found no clear evidence of more rapid decline among the elderly, a 2010 study noted a statistically significant decline in titers 6 months post-vaccination among persons aged ≥65 years (although titers still met European Medicines Agency levels considered adequate for protection).

- Bacterial pneumonia complicating influenza is well-recognized as a severe manifestation of influenza. Influenza-associated bacterial pneumonia remains a major contributor to the burden of influenza.*