

## Shifts in the Treatment of Community Acquired Pneumonia

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Community-acquired pneumonia (CAP) is defined as a newly recognized pulmonary infiltrate with two or more symptoms that is acquired outside of the hospital setting. Empiric antibiotic treatment has traditionally centered around coverage for *Streptococcus pneumoniae* (*S. pneumoniae*). However, the proportion of cases attributable to *S. pneumoniae* has steadily declined over time since the use of the pneumococcal vaccine (5-15% of cases of CAP). Furthermore, a significant proportion of cases (20-25%) may be caused by respiratory viruses and there is ongoing debate about the need to cover for atypical pathogens.<sup>1</sup>

In late 2019, the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) updated the guideline for the diagnosis and treatment of adults with community-acquired pneumonia (CAP) for the first time since 2007.<sup>2</sup> The new guideline focuses on 16 specific areas for recommendations in diagnostic testing, appropriate site of care, initial empiric antibiotic therapy and consequent treatment decisions. The purpose of this newsletter is to discuss key changes in the management of CAP based on recent guidelines.

### Removal of Health care-associated pneumonia (HCAP)

Health care-associated pneumonia (HCAP) was included in previous guidelines to identify patients at risk of pneumonia from multidrug-resistant pathogens due to exposure to various healthcare settings (nursing homes, dialysis centers, wound care, etc.). It was recommended to broaden empiric treatment for patients with HCAP and treat similar to hospital acquired pneumonia. Since then, studies have shown the risk factors used to define HCAP do not accurately predict the presence of multidrug resistant pathogens.<sup>2</sup> Additionally, this resulted in increased use of broad-spectrum antibiotics with no improvement in patient outcomes.<sup>2</sup>

The updated guideline removed the HCAP designation and instead recommends broadening coverage for methicillin resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* (*P. aeruginosa*) in adults with CAP only if locally validated risk factors are present.<sup>2</sup> The strongest risk factors are prior isolation of these organisms and hospitalization (or long-term care facility) with exposure to parenteral antibiotics in the last 90 days. Other potential drug pathogens that exhibit multidrug resistance should also be considered (e.g. *Enterococcus faecium*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterobacter*). Lastly, it should be emphasized to deescalate broad spectrum antibiotic therapy at 48 hours consistent with microbiological results.

**Table 1: Empiric Outpatient CAP Therapy<sup>2</sup>**

Healthy Outpatients without comorbidities	Outpatients with comorbidities
<ul style="list-style-type: none"> <li>Amoxicillin 1gm TID, or</li> <li>Doxycycline 100 mg BID</li> </ul>	<ul style="list-style-type: none"> <li>Amoxicillin/clavulanate OR a cephalosporin PLUS a macrolide or doxycycline, or</li> <li>Respiratory fluoroquinolone*</li> </ul>
*levofloxacin 750 mg daily, moxifloxacin 400 mg daily	

### Role of macrolides

The 2007 CAP guidelines included a strong recommendation for macrolide monotherapy for outpatients without comorbidities. In contrast, the updated guidelines include macrolide monotherapy as a conditional recommendation based on the local resistance of your area (< 25%) of *S. pneumoniae* to macrolides.<sup>2</sup> However, resistance is around 30% in most of the United States (including Oregon) and macrolide monotherapy should be discouraged in this patient population.<sup>3</sup> Furthermore, high dose amoxicillin (1 gm three times daily) is recommended for adults without comorbidities (Table 1). The higher dose overcomes resistant *S. pneumoniae* and studies have demonstrated efficacy of

this regimen despite the lack of coverage for atypical organisms. An alternative to amoxicillin is doxycycline (Table 1).

Patients with comorbidities (chronic heart, lung, liver or renal disease; diabetes; alcoholism; malignancy) are more likely to experience poor outcomes if the initial antibiotic regimen is inadequate and may have risk factors for antibiotic resistance due to increased exposure to the healthcare system and/or prior antibiotic exposure. Therefore, the recommended regimen in the outpatient setting is a  $\beta$ -lactam (amoxicillin/clavulanate, cefpodoxime, or cefuroxime) in combination with either a macrolide or doxycycline (Table 1), with only low quality evidence supporting doxycycline.<sup>2</sup> An alternative strategy is monotherapy with a respiratory fluoroquinolone. These combination regimens should adequately cover macrolide- and doxycycline-resistant *S. pneumoniae* since  $\beta$ -lactam resistance is less common. It also covers atypical pathogens of interest, many enteric gram-negative bacilli and methicillin-susceptible *Staphylococcus aureus* (MSSA), and the addition of clavulanate provides coverage against  $\beta$ -lactamase producing *Haemophilus influenzae*. Due to safety concerns (e.g. tendinopathy, peripheral neuropathy, significant hypoglycemia, central nervous system effects, and aortic aneurysm rupture) with fluoroquinolones, they should be reserved for situations when  $\beta$ -lactams are not an option. If a patient has received an antibiotic within the previous 90 days, an antibiotic from a different class should be considered.

### Empiric Therapy for Severe CAP

Empiric treatment for adult inpatients with nonsevere CAP and without risk factors for MRSA or *P. aeruginosa* remain largely unchanged since the 2007 guidelines (Table 2). The combination of a  $\beta$ -lactam (e.g. ampicillin/sulbactam, ceftriaxone, ceftaroline) with a macrolide OR monotherapy with an antipneumococcal fluoroquinolone is recommended.<sup>2</sup> Preference is not given to one regimen over the other since data from noninferiority trials have demonstrated similar efficacy with  $\beta$ -lactam/macrolide therapy compared to fluoroquinolone monotherapy. However, providers should consider the Food and Drug Administration (FDA) safety warnings associated with fluoroquinolones.

For inpatient adults with severe CAP, the updated guidelines cited higher quality evidence for the combination of a  $\beta$ -lactam and a macrolide (moderate quality evidence) compared to a  $\beta$ -lactam plus a respiratory fluoroquinolone (low quality evidence).<sup>2</sup> This minor change is supported by a possible mortality benefit seen with regimens including a macrolide in observational data.

Coverage for MRSA and/or *P. aeruginosa* should be added in patients with prior respiratory isolation and in those with recent hospitalization and parenteral antibiotics. Nasal PCR has a 99% negative predictive value and can be used to deescalate MRSA coverage. Only one antipseudomonal  $\beta$ -lactam is needed for those with risk factors for *P. aeruginosa*.

**Table 2: Empiric Inpatient CAP Therapy<sup>2</sup>**

Inpatients (non-severe) without risk factors for MRSA or <i>P. aeruginosa</i>	Inpatients (severe*) without risk factors for MRSA or <i>P. aeruginosa</i>
<ul style="list-style-type: none"> <li><math>\beta</math>-lactam (ampicillin/sulbactam or ceftriaxone) PLUS macrolide, or</li> <li>Respiratory fluoroquinolone</li> </ul>	<ul style="list-style-type: none"> <li><math>\beta</math>-lactam (ampicillin/sulbactam or ceftriaxone) PLUS macrolide, or</li> <li><math>\beta</math>-lactam PLUS respiratory fluoroquinolone</li> </ul>
*Severe CAP includes either one major criterion (septic shock or mechanical ventilation) or three or more minor criteria (respiratory rate > 30, PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> ratio <250, multilobar infiltrates, confusion, uremia, leukopenia, thrombocytopenia, hypothermia, hypotension requiring fluid resuscitation)	

**Use of Corticosteroids**

The use of corticosteroids in CAP was not discussed in the 2007 ATS/IDSA guidelines. There are no data showing a benefit of corticosteroids in patients with nonsevere CAP and the updated guideline recommends against using corticosteroids in adults with nonsevere CAP (strong recommendation, high quality evidence).<sup>2</sup> They also do not recommended routine steroid use in severe CAP. However, this is only a conditional recommendation with low quality evidence based on inconsistent findings in the literature. While two randomized controlled trials (RCTs) demonstrated a reduction in mortality, length of stay, and organ failure, other RCTs have not shown an effect on clinically important outcomes and these results have not been replicated.<sup>2</sup> Results from published meta-analyses are also conflicting. With unclear data in severe CAP, the guideline does endorse the Surviving Sepsis Campaign recommendations for the use of corticosteroids in patients with septic shock refractory to fluid resuscitation and vasopressor support.<sup>2</sup>

**Table 3: Summary of Changes to Treatment Recommendations<sup>2</sup>**

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
<b>Macrolide monotherapy</b>	Strong recommendation for outpatients	Conditional recommendation for outpatients based on local resistance rates
<b>Empiric therapy for severe CAP</b>	β-lactam PLUS macrolide and β-lactam PLUS fluoroquinolone given equal weighting	Stronger evidence in favor of β-lactam/macrolide combination
<b>Use of HCAP Category</b>	Accepted as per 2005 hospital-acquired pneumonia guidelines	Remove HCAP and focus on local epidemiology and validated risk factors for MRSA and <i>P. aeruginosa</i>
<b>Use of corticosteroids</b>	Not covered	Not universally recommended, consider in patients with septic shock

**Aspiration Pneumonia**

Aspiration pneumonia occurs with large-volume aspiration of colonized oropharyngeal or upper gastrointestinal contents leading to an infection. It is estimated that aspiration pneumonia causes 5-15% of CAP cases.<sup>4</sup> Risk factors include dysphagia; head, neck and esophageal cancer; chronic obstructive pulmonary diseases, impaired consciousness and seizures. The predominant pathogens in aspiration pneumonia were historically anaerobes. More recent studies have shown anaerobes are uncommon in patients with aspiration pneumonia. Instead, bacteria usually associated with CAP (*S. pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Enterobacteriaceae*) have been shown to be the main isolates in patients with aspiration pneumonia.<sup>4</sup>

Additionally, typical CAP coverage is active against the majority of gram-positive anaerobes found in the oropharyngeal tract. Additional anaerobic coverage would only be necessary if gram-negative anaerobes from the gastrointestinal tract were suspected. Taking these things into account, the updated guidelines do not recommend routinely adding anaerobic coverage for aspiration pneumonia unless lung abscess or empyema is suspected.<sup>2</sup>

**Duration**

The guidelines recommend antibiotics for a minimum of 5 days and until the patient achieves clinical stability (normal vital signs, ability to eat and normal mentation).<sup>2</sup> Several small randomized trials with shorter courses of 5 days are noninferior to 7-8 days for the treatment of CAP.<sup>2</sup> Longer treatment courses should be considered for pneumonia complicated by meningitis, endocarditis and other deep-seated infection or infection with other, less common

pathogens. Additionally, patients who fail to achieve clinical stability within 5 days should be evaluated for resistant pathogens, additional complications of pneumonia, or alternative source of infection.

**Additional Diagnostic Updates**

Changes in diagnosis and testing recommendations were also made to the 2019 guidelines. Previously, sputum and blood cultures were primarily recommended for patients with severe disease. In addition to patients with severe disease, the updated guidelines recommend collecting sputum and blood cultures in patients being empirically treated for MRSA or *P. aeruginosa* and in those with risk factors for MRSA or *P. aeruginosa*.<sup>2</sup> The goal of these recommendations is to identify resistant pathogens, narrow therapy, adjust therapy when appropriate, and to continue evaluation of the everchanging epidemiology of CAP.

While not discussed in the 2007 guideline, the use of procalcitonin is not recommended to determine the need for antibiotic initiation in the current guidelines. The literature regarding its ability to accurately distinguish between viral and bacterial etiology is mixed. If used to assist in the diagnosis and treatment of bacterial infection, appropriate protocols and education are needed to establish antibiotic de-escalation interventions. The guidelines reinforce that empiric antibiotics are recommended if CAP is clinically suspected and radiographically confirmed, regardless of procalcitonin level.

Lastly, the ATS/IDSA guideline update does not recommend routine use of follow-up chest imaging in patients whose symptoms have resolved and *Legionella* and Pneumococcal urinary antigen testing is not recommended for the majority of adults with CAP.

**Conclusion**

A summary of recent changes to the ATS/IDSA guideline for CAP is included in **Table 3**. The preferred regimens continue to focus on β-lactams with or without a macrolide depending on level of care and comorbidities. Due to a myriad of potential adverse effects, fluoroquinolones should be reserved for when a β-lactam is not an option. Changes in microbiologic patterns include more respiratory viruses contributing to CAP, increasing *S. pneumoniae* resistance to macrolides, and the fewer anaerobic pathogens contributing to aspiration pneumonia. Although several antibiotics have been FDA approved for CAP more recently (delafloxacin<sup>5</sup>, lefamulin<sup>6</sup> and omadacycline<sup>7</sup>), the place in therapy of these agents is limited at this time until more data is available.

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