Management of Pneumonia Syndromes in the Hospital: Make Pneumonia Your Best Friend

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KEYWORDS
- Pneumonia ● Community-acquired pneumonia ● Hospital-acquired pneumonia
- Ventilator-associated pneumonia ● Aspiration pneumonia ● Antibiotics

KEY POINTS
- Viruses may cause CAP more commonly than previously recognized, although the causative organism is rarely identified.
- The diagnosis of CAP remains clinical. Given the limitations of CXR, point-of-care ultrasound and chest CT scanning can be used as adjuncts.
- In the treatment of CAP in the hospital, risk factors for MRSA and Pseudomonas aeruginosa can help guide empiric therapy; these include patients with either prior isolation of the organism or receipt of parenteral antibiotics in the prior 90 days.
- Most patients hospitalized with CAP should receive 5 days of antibiotic therapy; those with HAP or VAP should receive 7 days of therapy.
- Treatment of HAP and VAP should generally include coverage of MRSA and resistant gram-negative organisms.

Pneumonia may well be called the friend of the aged. Taken off by it in an acute, not often painful illness, the old man escapes those “cold gradations of decay” so distressing to himself and his friends.

—William Osler, 1898

INTRODUCTION

Pneumonia syndromes are defined as acute infections of the pulmonary parenchyma. The most common pneumonia syndromes in the hospital include:

- Community-acquired pneumonia (CAP): acquired outside of the hospital setting
• Hospital-acquired pneumonia (HAP): acquired ≥48 hours after admission to the hospital
• Ventilator-associated pneumonia (VAP): acquired ≥48 hours after endotracheal intubation
• Aspiration pneumonia: acquired outside or inside the hospital setting after inhalation of gastric contents

Pneumonia syndromes cause significant morbidity and mortality. This article provides a comprehensive review of the common syndromes with a particular focus on CAP.

COMMUNITY-ACQUIRED PNEUMONIA

Microbiology

The understanding of the microbiology of CAP has evolved in recent years. Classic teaching held that most CAP was caused by typical bacteria (eg, *Streptococcus pneumoniae*) with some contribution from atypical bacteria (eg, *Mycoplasma* spp). Recent evidence suggests the microbiology may be more complex with increasing contributions from respiratory viruses.

A large study evaluated patients admitted to the hospital with CAP with a broad array of diagnostic tests including blood and sputum cultures, urine antigen testing, and any available polymerase chain reaction testing. The authors failed to detect a pathogen in 62% of patients. The following pathogens were identified:

- A virus (23%)
- A bacteria (11%)
- Both (3%)

Rhinovirus (9%), influenza (6%), and *S pneumoniae* (5%) were the most frequently identified. Atypical pathogens were identified in only 4%. The authors posited few sputum specimens and the adoption of the childhood pneumococcal vaccine as reasons for the low overall yield and the low rate of *S pneumoniae*, respectively.

In an alternative study, molecular testing resulted in pathogen detection in 87% of patients, which included bacteria in 81%, virus in 30%, and coinfection with both in 24%. Common CAP bacterial pathogens predominated (eg, *S pneumoniae*).2

As diagnostic testing improves, the understanding of the microbiology will evolve. The evidence does suggest viruses play a prominent role but the usual bacterial organisms are still commonly present.

Concern has been raised about the rising prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) as a cause of severe CAP. Studies have revealed community-acquired MRSA is actually uncommon; it may be the causative agent in less than 3% of cases.3 Certain risk factors can increase the likelihood of MRSA (Box 1) and these risk factors need to be considered when deciding on appropriate empiric therapy.

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Risk factors for infection from MRSA or <em>Pseudomonas aeruginosa</em></th>
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<td>Patients with either of the following:</td>
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<td>• Prior respiratory isolation of the organism</td>
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<td>• Received parenteral antibiotics within the prior 90 days</td>
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In real-world settings, the causative organism is not identified in most patients with CAP. Given the limitations of the standard diagnostic tests, empirical therapy must target typical and atypical organisms and, when relevant, influenza infection.

Lastly, the fundamental understanding of the microbiology of the lungs is changing. The pulmonary parenchyma has long been presumed to be a sterile space. Yet, recent work suggests CAP may be increasingly understood as a dysbiosis (an imbalance in the types of organism present in an individual’s natural microflora). The implications of such an understanding are difficult to predict but could fundamentally change how one thinks about the treatment of CAP.

**Diagnosis**

The diagnosis of pneumonia remains clinical, based on a combination of:

- Signs or symptoms of pneumonia (which can include fever, confusion, new or worsening cough, sputum production, dyspnea, etc.) and
- Evidence of new pulmonary infiltrate on imaging

Unfortunately, there are no historical features or examination signs that are accurate enough to make the diagnosis of CAP without imaging.

**Imaging**

The 2019 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) CAP guidelines emphasize that the diagnosis of pneumonia has a radiographic component but do not comment on a preference for a particular imaging modality. The chest radiograph (CXR) remains the most frequently used diagnostic test but has limitations. A 2012 study enrolled 3423 patients who presented to the emergency department with at least one of shortness of breath, chest pain, or cough. All patients received CXR and chest computed tomography (CT). They found that CXR was 43.5% sensitive and 93% specific for pulmonary opacity. In a smaller 2015 study that evaluated patients specifically suspected of CAP who received a chest CT within 4 hours, CXR performed poorly. CT scans revealed an infiltrate in 33% of patients with no infiltrate on CXR and excluded CAP in 30% of patients with an infiltrate on CXR. In a patient with consistent symptoms, a clear infiltrate on CXR likely does indicate pneumonia but absence does not reliably rule out the diagnosis.

Point-of-care ultrasound is an increasingly used modality to diagnose CAP. When chest CT is used as a reference, bedside ultrasound has a sensitivity of 85% to 95% and a specificity of 75% to 90%. Overall performance is believed to be better than CXR. An important limitation is the need for provider expertise in the acquisition and interpretation of images. As the technology and skill become more ubiquitous, point-of-care ultrasound may become an important modality in the diagnosis of CAP.

Chest CT is usually used as the reference standard to delineate pulmonary infiltrates. That said, it is not always clear when to order a CT scan and the decision to do so is highly provider dependent. We recommend chest CT when there is one of the following:

- High clinical suspicion of pneumonia but a negative CXR
- Suspicion of a false-positive CXR
- Suspicion of an alternative diagnosis (eg, pulmonary embolism)
- To evaluate for potential causes of treatment failure (eg, abscess or empyema)

Patterns of CT use may change in the next decade as protocols with less radiation exposure and lower cost become available.
Procalcitonin

There is increasing interest that procalcitonin can be used in CAP (and other diseases) to help differentiate bacterial infections from other infections. Multiple studies have shown that procalcitonin is elevated in bacterial infections and low or normal in viral or other infections.11 Hope has persisted that procalcitonin might discriminate a population of patients with pneumonia who are unlikely to have a bacterial cause and so can reasonably be spared antibiotic therapy. A decrease in procalcitonin level has also been studied to identify patients for whom antibiotics might be stopped early.

Although procalcitonin has demonstrated promise, the 2019 IDSA/ATS CAP guidelines recommend against its use in patients who are believed to have CAP.7 This is based on several key factors:

- Poor at ruling out atypical bacterial infections and mixed bacterial and viral infections
- Inability to adequately rule out bacterial infection at the time of presentation (antibiotics must be initiated if the patient has clinical pneumonia)
- Unlikely to reduce antibiotic exposure if used to decide about stopping antibiotics given recommendations for shorter courses of antibiotics (discussed in Treatment section)

Other Studies

In most patients hospitalized for CAP, the causative organism cannot be identified even with appropriate diagnostic testing.4 The 2019 IDSA/ATS CAP guidelines strongly recommend attempts to identify a causative organism in two cohorts of patients7:

- Those with risk factors for MRSA and/or Pseudomonas aeruginosa (see Box 1)
- Patients with severe CAP (Box 2)

In these patients, blood and sputum cultures are recommended. Note, in other patients hospitalized with CAP who do not meet these criteria, blood and sputum cultures should not routinely be ordered. They are unlikely to yield an organism and

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**Box 2**

Criteria for defining severe community-acquired pneumonia

Definition includes either 1 major criteria or 3 or more minor criteria

**Minor criteria**
- Respiratory rate greater than 30 breaths/min
- Pao₂/Fio₂ ratio less than 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia
- Leukopenia
- Thrombocytopenia
- Hypothermia
- Hypotension requiring intravenous fluids

**Major criteria**
- Septic shock with need for vasopressors
- Respiratory failure requiring ventilation

the risk of identifying organisms because of contamination (and confusion) is high.\textsuperscript{7} The guidelines also recommend not routinely sending urine pneumococcal antigen or urine \textit{Legionella} antigen as there are flaws with the test characteristics and utility of both tests.\textsuperscript{7}

\textbf{Treatment}

\textbf{Treatment overview}

Despite advances in the understanding of the microbiology of CAP, there remain significant challenges in real-world settings in identifying causative agents and patients at increased risk for antibiotic-resistant pathogens. As such, treatment remains largely empiric. Prior guidelines and the overly inclusive category of health care–associated pneumonia (HCAP) led to vast overuse of unnecessarily broad-spectrum antibiotics in the past decade without evidence of improved outcomes.\textsuperscript{12}

A concerted effort toward antibiotic stewardship motivated the 2019 ATS/IDSA update to suggest multiple changes as follows:\textsuperscript{7}:

- Doing away with HCAP classification
- A preference for shorter courses of antibiotics
- Avoiding anaerobic coverage for aspiration
- Choosing broad-spectrum coverage based on local and individualized epidemiologic data and validated severity indices

\textbf{General treatment strategies}

Established sepsis guidelines and large, multicenter studies of patients with CAP suggest benefit from a standardized approach (eg, care bundles) to CAP treatment. These bundles can include rapid and adequate fluid resuscitation, risk stratification, early measurement and correction of hypoxia, early ambulation, and maintenance of electrolyte and glucose homeostasis.\textsuperscript{13} Institutions are encouraged to develop such bundles and incorporate them into the electronic medical record.

\textbf{Antibiotics and treatment hierarchy}

Selection of an antibiotic regimen in CAP continues to be guided by location (outpatient, inpatient, intensive care unit [ICU]), comorbidities, risk factors for resistant organisms, and disease severity.\textsuperscript{7} The guideline-recommended antibiotic regimens for outpatients with CAP are beyond the scope of this review but are found in the IDSA/ATS guidelines.\textsuperscript{7}

\textbf{Treatment of inpatient community-acquired pneumonia}

For inpatients, empiric regimens are guided by severity of illness and risk factors for resistant organisms. The most recent guidelines suggest using previously described criteria for severe CAP (see Box 2).\textsuperscript{5,7} Although we agree with these criteria, in practical management, “severe CAP” is more easily defined by the presence of any of the following:

- Septic shock
- Respiratory failure requiring mechanical ventilation
- Other factors requiring ICU admission

\textbf{Nonsevere community-acquired pneumonia}

For nonsevere CAP (ie, non-ICU), the single most optimal regimen remains unclear despite large, multicenter trials and subsequent meta-analyses. Overall, the evidence supports antibiotic selection that empirically treats traditional typical and atypical organisms.\textsuperscript{14}

The guidelines suggest three potential regimens to treat nonsevere CAP (Box 3):
Combination β-lactam (eg, ceftriaxone) plus macrolide (eg, azithromycin)
Monotherapy with a respiratory fluoroquinolone (eg, levofloxacin)
Combination β-lactam plus doxycycline (most useful for patients with both macrolide and fluoroquinolone intolerance)

In selecting one regimen over others, hospital-based providers should consider using local antibiograms and prescribing patterns. Of note, a recent study suggests doxycycline may have a lower incidence of *Clostridium difficile* infection in the setting of CAP requiring hospitalization. Doxycycline may also have lower out-of-pocket costs for patients.

Severe community-acquired pneumonia
In general for severe CAP, the microbiology is the same as nonsevere CAP. Yet, patients with severe pneumonia are most likely to have resistant organisms and broader coverage can be considered. Combination therapy is standard. Guidelines-recommended regimens include

- A β-lactam plus a macrolide or
- A β-lactam plus a respiratory fluoroquinolone

We prefer a β-lactam plus a macrolide because a meta-analysis of observational data favors macrolide-containing regimens based on a potential mortality benefit when compared with other regimens. The ATS/IDSA guidelines suggest including a macrolide when treating severe CAP and caution against fluoroquinolone monotherapy or combination β-lactam/doxycycline. All patients with severe CAP should have blood and sputum cultures. Empiric treatment of MRSA (eg, vancomycin) and *P aeruginosa* (eg, piperacillin/tazobactam) is not necessary for all patients with severe CAP. This decision should be reserved for patients with specific risk factors (see Box 2).

Response to treatment
Typically, significant clinical response is expected within 24 to 48 hours after initiation of antibiotic therapy. Clinical worsening or slow/absent response should quickly raise suspicion for a resistant organism, an atypical organism, a complication of pneumonia (eg, empyema), or an alternative diagnosis (eg, interstitial lung disease). Moreover, symptoms can persist; in one study of the natural history of CAP, nearly 90% of patients had at least one pneumonia-related symptom (eg, cough, shortness of breath, chest pain) at 30 days. This information is important when counseling patients at the time of discharge.
**Duration of therapy**

A growing body of evidence continues to suggest noninferiority of shorter regimens compared with longer regimens. A randomized controlled trial in 2016 showed that in hospitalized patients with nonsevere CAP who had clinically improved and were afebrile after 48 hours, treatment with 5 days had similar mortality and clinical response to a longer course (approximately 10 days).\(^{19}\) Based on this and other prior studies, the new 2019 IDSA/ATS CAP guidelines recommend treatment for 5 days for most patients.\(^7\) One caveat is patients must be clinically improved and afebrile. Some patients with CAP are slower to respond and may need 7 days of therapy. Nearly 30% of patients in the previously mentioned randomized controlled trial received more than 5 days based on the discretion of the provider.\(^{19}\) Extension to 7 days should also be considered for those with suspected or proven MRSA or pseudomonal CAP.\(^7\) Decesalation to regimens with narrower antimicrobial spectra is guided by any available microbiologic data.

For future directions, initial studies have shown promise for the antimicrobials omadacycline (a tetracycline) and lefamulin (a novel pleuromutilin antibiotic) for CAP, although high cost and sparse safety data limit their current utility.

**Adjunctive Treatments**

**Corticosteroids**

In patients with CAP, some of the lung injury that can lead to respiratory failure is not from the causative organism but rather from the host’s inflammatory response. With this understanding, multiple studies investigating the utility of systemic corticosteroids in CAP have been performed, leading to several large meta-analyses and systematic reviews.\(^{20–23}\) Overall, these collectively suggest a possible reduction in length of stay, antibiotic duration, and perhaps even mortality with an increase in hyperglycemia. Yet the data are heterogeneous and of only low-to-moderate quality. Based on this, the most recent ATS CAP guidelines recommend against routinely using corticosteroids in the treatment of CAP.\(^7\)

Given the overall data and a potential for real clinical and survival benefits, the authors believe it is reasonable to consider using adjunctive steroids for patients with severe CAP. Specific steroid, dose, and duration varied across the major studies but based on the largest study, a proposed regimen is prednisone 50 mg/d (or equivalent in methylprednisolone) for 7 days.\(^{20}\)

**Antiviral therapy**

Viruses are often discovered in patients presenting with CAP. Yet, the pathogenicity of these viruses and the possibility of coinfection with bacteria make interpretation of these results challenging. It is not clear that if a virus (eg, respiratory syncytial virus) is identified in a patient with CAP, it is safe to stop empiric antibacterial therapy. In the hospital setting, given morbidity and mortality associated with not treating bacterial pneumonia, it is typically appropriate to continue the antibacterial treatment in this situation.

During influenza season, empiric oseltamivir should be initiated in patients presenting with CAP. In patients with identified influenza pneumonia, treatment with oseltamivir likely leads to more rapid clinical improvement and lower mortality.\(^{24}\) The ATS/IDSA guidelines suggest there may be a role for premature cessation of antibiotic therapy in patients with CAP and confirmed influenza who improve rapidly after initiation of antiviral therapy.\(^7\) This decision can be made at the providers discretion based on the clinical circumstances.
**Miscellaneous**

**Cardiovascular disease**
The observational relationship between hospitalization for CAP and subsequent Cardiovascular disease has been well-established. The association includes an increased risk for myocardial infarction, stroke, and fatal coronary heart disease. A growing body of retrospective research has begun to explore whether concomitant antiplatelet or statin therapy might offer benefit in reducing the incidence of these comorbid outcomes. Prospective studies are needed to further investigate this high-risk area of overlap and to determine whether there is a role to initiate these agents de novo for patients hospitalized with CAP.

**HEALTH CARE–ASSOCIATED PNEUMONIA**
ATS guidelines published in 2005 defined a new category of pneumonia: HCAP. Research had revealed higher prevalence of resistant organisms in patients with health care exposure. In the guideline, patients were classified as having HCAP if they had one of the following: hospitalization in the previous 90 days, residence in a nursing facility, hemodialysis, or receipt of homecare (eg, antibiotics, wound care). Since the publication of these guidelines, extensive evidence has revealed these criteria do not accurately predict antibiotic-resistant pathogens and this classification has led to excessive use of broad-spectrum antibiotics with no impact on outcomes. Because of this, HCAP was not included in the most recent HAP/VAP guidelines and is no longer viewed as a valid classification of pneumonia type. Instead, in a patient with CAP, the decision about coverage of resistant organisms (eg, MRSA, *P aeruginosa*) should be based on the individual risk factors that are strongly predictive (see Box 1) and local microbiology (eg, high prevalence of MRSA causing CAP requiring ICU admission).

**HOSPITAL-ACQUIRED PNEUMONIA AND VENTILATOR-ASSOCIATED PNEUMONIA**
HAP and VAP are associated with morbidity, resource use, and mortality. HAP is defined as “pneumonia not incubating at the time of admission, and occurring greater than 48 hours from admission,” whereas VAP is similarly defined as “pneumonia occurring greater than 48 hours after endotracheal intubation.”

**Microbiology and Diagnosis**
Prevalent pathogens in HAP and VAP differ considerably from those in routine CAP and include: *S aureus* (methicillin-sensitive and methicillin-resistant), *P aeruginosa*, and other enteric gram-negative bacilli. *S pneumoniae*, a dominant pathogen in CAP, may contribute to HAP outside the ICU.

The gold standard for diagnosis of HAP and VAP remains elusive. In general, clinical and radiographic evidence of pneumonia should lead the clinician to obtain noninvasive microbiologic tests of disease. These include blood cultures and sampling of respiratory secretions, whether from produced or induced sputum in HAP or nasotracheal/endotracheal aspiration in VAP (or HAP patients who are subsequently ventilated).

**Treatment**
As in CAP, treatment of HAP or VAP begins with careful risk stratification. Recent guidelines encourage clinicians to incorporate the following to determine the need for empiric therapy against multidrug-resistant organisms (MDRO):
Empiric therapy for HAP and VAP should generally include coverage for *S. aureus* and for gram-negative rods. Selection of specific antibiotic regimens depends on risk factors for MRSA and risk factors for drug-resistant gram-negatives. Risk factors for MRSA in the setting of HAP and VAP include:

- Treatment in a unit where greater than 10%–20% of *S. aureus* isolates are methicillin-resistant
- Treatment in a unit where the prevalence of MRSA is not known
- Colonization with MRSA or prior isolation of MRSA

Risk factors for multidrug-resistant gram-negative organisms in the hospital include:

- Intravenous antibiotic use within the previous 90 days
- Septic shock at the time of HAP/VAP
- 5 days of hospitalization before the occurrence of HAP/VAP
- Acute renal-replacement therapy before HAP/VAP onset

Patients with HAP or VAP without MRSA or MDRO risk factors can generally be treated with monotherapy including: piperacillin-tazobactam, cefepime, imipenem, or meropenem. If patients have MRSA risk factors, then vancomycin or linezolid should be added. If a patient with HAP or VAP is critically ill or has MDRO risk factors, clinicians should consider treating with two gram-negative agents. Providers can choose from two of the following: piperacillin-tazobactam, cefepime, levofloxacin, imipenem or meropenem, tobramycin, or aztreonam.

**De-escalation**

The recent guidelines emphasize prompt species identification and early transition to narrowed, tailored regimens when possible. Yet, similar to CAP, often the causative organism cannot be identified in patients with HAP or VAP. Under these circumstances, if a patient is clinically improving, in general the antibiotics should be de-escalated, that is, changed to a more narrow-spectrum antibiotic or to monotherapy if treated with multiple agents.

A recent retrospective study showed shorter length of stay, lower acute kidney injury, and no difference in mortality when patients with HAP or VAP without an identified organism had *S. aureus* coverage discontinued by Day 4. In patients with HAP or VAP with unknown microbiology who are clinically improving, in general providers should stop the *S. aureus* coverage on Day 3 and can often transition to an oral fluoroquinolone shortly thereafter.

**Duration of Therapy**

A typical regimen for either HAP or VAP should be for at least 7 days, although regimens may be reasonably abridged (rarely to fewer than 5 days) or extended based on provider discretion. Neither procalcitonin nor clinical pulmonary infection score are recommended to guide initiation or duration of therapy.

**ASPIRATION**

Aspiration of small amounts of oropharyngeal contents is common; in one study, 45% of healthy adults had some aspiration while sleeping. In patients with depressed
consciousness, dysphagia, or other risk factors, aspiration of larger amounts of material can lead to several aspiration syndromes:

- Aspiration pneumonitis
- Aspiration pneumonia
- Pulmonary abscess

When gastric contents (eg, vomit, undigested food, liquids) are aspirated, the initial response is a chemical pneumonitis, a noninfectious inflammatory response. Pneumonitis can present with fever, cough, wheezing, or hypoxia, and in rare cases can lead to acute respiratory distress syndrome. Patients typically recover over the course of hours and typically do not need antibiotic therapy.

True aspiration pneumonia typically develops 48 to 72 hours after the aspiration event, which represents the time necessary for bacterial replication, and can present with respiratory symptoms or nonrespiratory symptoms in the elderly (eg, confusion, falls). It was a long-standing belief that anaerobes were the main organism involved in true aspiration pneumonia. Studies have revealed this is not the case and that, for most patients with true aspiration pneumonia, the microbiology is similar to the microbiology of CAP or HAP. Although there is not clear evidence, most patients with true aspiration pneumonia can be treated similar to patients with CAP and HAP (discussed in Treatment and HAP/VAP sections).

Pulmonary abscess is a unique clinical scenario where the presentation is more indolent; patients typically present weeks to a month after the aspiration events. Symptoms typically include low-grade fever, cough with purulent sputum, and general malaise. Pulmonary abscesses are often polymicrobial, including anaerobes. Therefore, therapy should include anaerobic coverage; a β-lactam with a β-lactam inhibitor is appropriate.

SUMMARY

Pneumonia syndromes are common in hospital medicine and lead to substantial morbidity and mortality. The evidence and guidelines provide clear recommendations on management strategies. Future research will provide more insight into the microbiology, optimal diagnostic testing, and best therapeutic options for these syndromes.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES


