

Pneumonia: Introduction

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Pneumonia, along with influenza, is the leading cause of death from infectious diseases and overall is the eighth leading cause of death. Newly recognized pathogens, emergence of organisms highly resistant to antibiotics and novel clinical scenarios present ongoing challenges for diagnosis, treatment and prevention of lower respiratory tract infections. In recent years, epidemiologic and microbiologic studies have clearly delineated different paradigms. Recognition of the organisms most likely responsible for community acquired pneumonias and healthcare associated pneumonias have allowed the development of rational choices for empiric therapy for each setting. These have been promulgated in guidelines by national subspecialty organizations and are reviewed in articles by Al-Qadi et al. and by Silverblatt. The recent pandemic of novel H1N1 influenza has served to remind us of the potential devastating consequences of this infection. The history of the great influenza pandemic of 1918 and a review of what we have learned with the current outbreak is covered by Irizarry and Puius. Finally, Penelope Dennehy reviewed pneumonias in the pedi-

atric population. Despite advances in understanding the pathogenesis, etiology and improvement in diagnostic and therapeutic modalities, pneumonia remains a significant clinical problem. Renewed appreciation of this illness should be of interest to clinicians in all medical disciplines.

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Community Acquired Pneumonia

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Pneumonia, along with influenza, is the eighth leading cause of death in the United States.¹ Pneumonia is common within all age ranges and comprises a significant cause of mortality, particularly in elderly individuals.^{2,3} Although the introduction of antibiotics substantially reduced the mortality associated with pneumonia, significant mortality persists. This is likely due to host factors such as worsened prognosis and risk of aspiration associated with advancing age, increasing populations of immune-suppressed individuals and to pathogen-related factors such as antibiotic resistance and constantly evolving virulence mechanisms. In recent years clinicians have distinguished **community acquired pneumonia (CAP)** from those acquired in a **health care facility (HCAP)** because the difference in likely pathogens in each setting facilitates rational empiric choice of antibiotics. In this article we discuss the causes, diagnosis and treatment of CAP.

RISK FACTORS

Microorganisms gain entry into the lower respiratory tract through two common routes, micro aspiration of nasopha-

ryngeal contents and direct inhalation of airborne microbial pathogens. Hematogenous spread of the organism to the lung is another less common source of acquiring CAP. In order to cause pneumonia, these organisms have to overcome numerous host defense mechanisms that protect the lung from infection. Impaired mucociliary function due to viral infections or tobacco smoking can cause damage to the ciliated respiratory epithelium. Impaired clearance of the organisms with excessive production of secretions accumulate in the alveoli, serving as an excellent media for bacterial growth. Influenza infection is one of the important predisposing factors to bacterial pneumonia, especially infection with *S. pneumoniae* and *S. aureus*. Disorders of mucociliary dysfunction (e.g. Kartagener's syndrome) or conditions associated with highly viscous and difficult to clear sputum (e.g. cystic fibrosis) predispose patients to recurrent pneumonia because of ineffective clearance of these secretions and increased colonization with resistant organisms, predominantly gram-negative bacteria and *S. aureus*.⁴ In addition, impaired cough reflex and epiglottal function be-

cause of swallowing difficulties (e.g. stroke) or altered level of consciousness due to seizure or alcohol intoxication will predispose patients to aspiration. Pneumonia following aspiration of nasopharyngeal contents is associated with an increase in the incidence of anaerobic infection. Patients with AIDS, hypocomplementemia, asplenia, hematologic malignancy (especially multiple myeloma), organ-transplant receiving immunosuppressant therapy, diabetes mellitus, and chronic kidney disease all have altered immune system and are at greater risk of developing pneumonia.⁵ Those individuals with immunodeficiency disorders are at risk of developing pneumonia from common respiratory pathogens and opportunistic pathogens.

ETIOLOGY

Despite the wide variation in etiology, *Streptococcus pneumoniae* remains the principal, causative pathogen of CAP worldwide. Although the organism responsible for CAP can be identified in only 40-50% of cases, several pathogens were recognized to cause CAP (Table 1)⁶

Table 1. The most common pathogens causing CAP

Organism	% of Cases
<i>Streptococcus pneumoniae</i>	20–60
<i>Haemophilus influenzae</i>	3–10
Gram-negative bacilli	3–10
<i>Legionella</i> spp.	2–8
<i>Chlamydophila pneumoniae</i>	4–6
<i>Mycoplasma</i> spp.	1–6
<i>Staphylococcus aureus</i>	3–5
Viral	2–15
Other (mixed anaerobes, <i>Moroxella</i> spp., Fungi, mycobacteria, etc.)	6–10

Streptococcus pneumoniae

S. pneumoniae has 91 recognized serotypes based on the polysaccharide capsular structure. However, most CAP cases are caused by few serotypes (1, 2, 3, 4, 7, 8, and 12), with serotypes 2 and 3 being considered the most virulent. The thick capsule of *S. pneumoniae* resists phagocytosis mediated by immunoglobulins and complement factors (C3b). Patients with hypogammaglobulinemia, multiple myeloma, sickle cell disease, and early complement deficiencies (C1, C2, C3, and C4) are rendered at great risk for developing severe and recurrent pneumococcal infections. Another virulence factor of *S. pneumoniae* is the exotoxin pneumolysin expressed by almost all pathogenic strains of *S. pneumoniae*. This potent cytotoxin causes lysis to host cells, impairment of epithelial ciliary function, and induces inflammation⁷. CAP caused by *S. pneumoniae* usually begins with a sudden, single rigor and might be associated with the characteristic rusty sputum. In addition, pneumococcal infection commonly involves the pleura causing pleurisy and parapneumonic effusion. Bacteremia, empyema and metastatic infections (e.g meningitis) are potential complications and should be considered if fever persists despite adequate treatment. (Figure 1)

H. influenzae

Both strains (Group B and non-typable) *H. influenzae* can cause CAP. The incidence of *H. influenzae* B infection has significantly decreased because of the vaccination in children with the HiB conjugate. Risk factors of *H. influenzae* infection include advance age, COPD, pregnancy, splenectomy, and HIV infection. Appropriate treatment of *H. influenzae* con-

sists of a respiratory fluoroquinolone, a macrolide, or a β -lactam- β -lactamase inhibitor combination (e.g. ampicillin-sulbactam) as *H. influenzae* is resistant to ampicillin in up to 40% of the cases.

Legionella pneumophila

The most common source of *Legionella* infection is inhalation of water droplets contaminated with this pathogen. Individuals at risk are elderly and immunocompromised patients. Clinically, it is usually associated with high fever, dyspnea, and variable extra pulmonary manifestations. These include myalgias, confusion, headache, diarrhea, and relative bradycardia.⁸ Classic laboratory findings include hyponatremia, hypophosphatemia, marked leukocytosis, and elevated transaminases. When suspected, the highly sensitive and specific urinary antigen should be used to confirm the diagnosis. Treatment usually consists of a macrolide, fluoroquinolone, or doxycycline.

Mycoplasma pneumoniae

Mycoplasma is a common cause of CAP, especially in young healthy people. It is usually acute in onset, starts with headache and fever, and dry cough develops later. Physical examination is usually out of proportion to the radiographic findings. Extra pulmonary manifestations are common (e.g. bullous

myringitis, Guillain-Barré syndrome, aseptic meningitis, and hemolytic anemia).⁹ Specific complement fixation test is recommended to make the diagnosis, as cold agglutinins are nonspecific. As in other atypical CAP, macrolides, or fluoroquinolones are usually appropriate therapies.

Chlamydophila pneumoniae

C. pneumoniae is responsible for 10% of all CAP cases. The clinical and radiographic manifestations are usually indistinguishable from CAP due to *Mycoplasma* spp. Patients usually present with dry cough associated with sore throat and fever. Upper and lower airways are involved, with hoarseness of voice and wheezing. *C. pneumoniae* is thought to play a role in the pathogenesis of coronary artery disease. Chest x-ray usually shows unilateral patchy infiltrate. Specific testing is usually not recommended, and treatment is usually empirical.

Community Acquired-MRSA

The incidence of CA-MRSA pneumonia is increasing. The virulence of these resistant strains of MRSA is related to the Panton-Valentine leukocidin protein and other virulence properties. CA-MRSA can cause severe necrotizing and hemorrhagic pneumonia. CA-MRSA should be anticipated in patients with cavitary CAP, severe CAP complicated by shock or respiratory failure, and in CAP preceded by



Figure 1. Anterior-Posterior view of a chest radiograph from a patient with severe pneumococcal pneumonia with bilateral infiltrates and a dense consolidation at the left mid lung field.

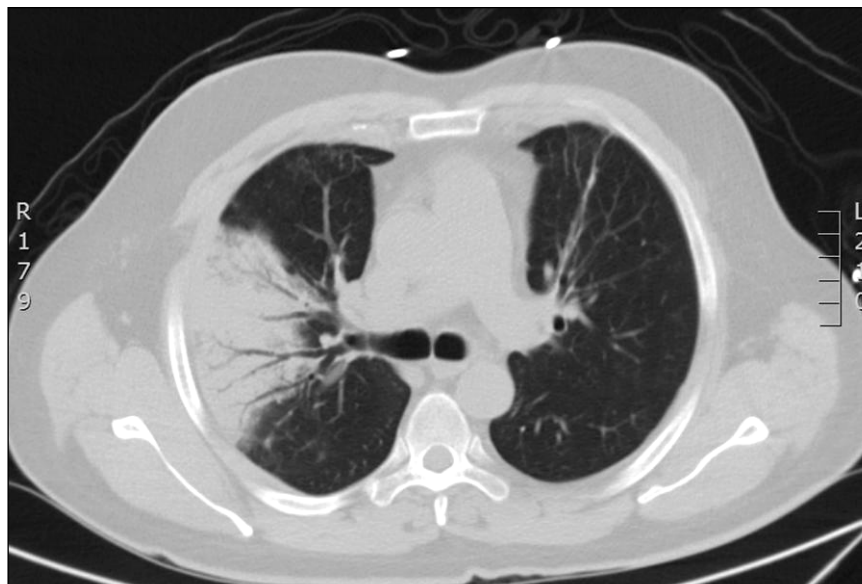


Figure 2. Computerized tomography of the lung showing a dense right sided infiltrate secondary to CAP from *S. aureus*.

influenza¹⁰. When CA-MRSA is suspected, vancomycin or linezolid should be included in the antibiotic regimen used for treatment. CA-MRSA is usually resistant to all β -lactams. Unlike nosocomial strains, CA-MRSA can be susceptible to clindamycin. (Figure 2)

Influenza and other Respiratory viruses

Viruses account for about 6% of CAP. This past year saw a pandemic of a novel H1N1 strain. Influenza and other respiratory viruses are considered in greater detail in accompanying articles in this issue.

DIAGNOSIS

Laboratory Workup

In young healthy individuals with mild CAP, few laboratory tests are usually required. **White blood count (WBC)**, **blood urea nitrogen (BUN)** and serum creatinine are helpful for the initial evaluation and to assess for the severity and hydration status of the patients. Blood culture is not required as part of the workup in mild CAP as would be seen in the outpatient setting. Only 10% of all hospitalized patients with CAP have positive blood cultures.¹¹ However, blood culture becomes essential in patients with severe CAP who require ICU admission and when antibiotic resistance is a concern. Pulse oximetry or ABG should also be done to evaluate for adequate oxygenation. Specific workup to identify the specific pathogen should not be done routinely. (Table 2) However, in the presence of epi-

demologic clues or if the clinical presentation is suggestive of an unusual organism, further testing is required.¹² Furthermore, testing for specific pathogen is crucial in patients with severe CAP as pathogen-directed therapy was associated with higher survival rate in ICU patients. In those patients, studies should include sputum (or endotracheal aspirate if intubated patient) culture, blood culture, and urinary antigen for *Legionella spp.* and *S. pneumoniae*¹³. Although the diagnostic yield of sputum Gram stain and culture is not high, negative results are usually sufficient to withhold broad-spectrum antimicrobial coverage (e.g. empiric coverage for MRSA and *P. aeruginosa*).

Sputum Gram stain and culture are also recommended for hospitalized patients who failed outpatient therapy, have structural lung disease or cavitary infil-

trate on chest x-ray, positive urine antigen test for pneumococcus or *Legionella spp.* and patients with pleural effusion.¹³

Radiography

The clinical diagnosis of CAP based on symptoms (chest pain, cough, and dyspnea) and signs (fever, tachycardia, and abnormal breath sounds) was unreliable compared to the combination of chest x-ray and clinical features.¹⁸ Chest radiographs are considered the cornerstone in the diagnosis of CAP. However, chest radiographs can be falsely-negative in patients with early (first 24 to 48 h) pneumonia, neutropenia, or dehydration. In addition, chronic radiographic changes (as in lung cancer, or congestive heart failure) may obscure of pneumonia infiltrates. Although the pattern of infiltrate on chest radiography is not a reliable predictor, it serves as a rough guide to possible microorganism causing CAP. (Table 3)¹⁹ The presence of a homogenous density that involves a distinct lobe of the lung (lobar pneumonia) and does not cross the fissures is suggestive of bacterial pneumonia. A bilateral patchy infiltrate usually indicates a bronchopneumonia where the infection extends along bronchi to adjacent areas and is not confined by the pulmonary fissures. Patients with immunodeficiency conditions (e.g. AIDS) are prone to unusual organisms which tend to primarily involve the interstitium, causing interstitial pneumonia and result in a diffuse granular infiltrate. Fungal infections usually result in diffuse reticulonodular opacities which may cavitate, and are associated with hilar and mediastinal lymphadenopathy. Septic emboli to the lung from right-sided endocarditis can also present with multiple nodular le-

Table 2: Diagnostic tests for CAP^{14,15,16, 17}

Diagnostic study	Sensitivity (%)	Specificity (%)
Pneumococcal urinary Antigen	50-80%	> 90%
Legionella Urinary antigen	70-90%	99%
Influenza antigen	50-70%	100%
Blood culture	5%-14%	—
Sputum culture	Yield 20-79%	Yield 20-79%
Sputum Gram stain		
Pneumococci	15-100%	11-100%
<i>Chlamydophila spp.</i>		
Rapid PCR (sputum, BAL)	30-95%	>95%
Serology	10-100%	
Other (<i>Mycoplasma</i> , <i>Chlamydophila</i> , <i>Legionella spp.</i> , Viral or fungal pathogens.		

Table 3: Radiographic findings and possible causative pathogens

Radiographic Pattern	Possible Pathogens
Lobar pneumonia	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>Legionella</i> spp.
Bronchopneumonia	Viral, <i>Mycoplasma</i> , <i>Chlamydia</i> spp., <i>S. aureus</i> .
Interstitial pneumonia	Influenza, CMV, <i>Pneumocystis jirovecii</i> , miliary TB.
Nodular lesions	Histoplasmosis, Coccidioidomycosis, Cryptococcosis, septic emboli
Cavitary lesions	Anaerobes (aspiration), <i>S. aureus</i> , Tuberculosis, Fungal, Nocardia.
"Bulging fissure" sign	<i>Klebsiella pneumoniae</i>
Wide mediastinum	Anthrax

sions which mimic pulmonary metastases. Cavitary lung lesions are commonly seen in patients with tuberculosis and alcoholics with aspiration pneumonia. Cavities result from tissue necrosis and are usually filled with necrotic material. (Figure 1)

High resolution computed tomography (HRCT) can be used to detect infiltrates in patients with structural lung disease (e.g. patients with malignancy). In addition, HRCT is superior to chest radiographs in patients with cavitary lesions or hilar lymphadenopathy.^{20, 21}

PROGNOSIS AND CLINICAL DECISION-MAKING

Mortality rates in patients with severe pneumonia have been reported as high as 28%. Approximately 10% of patients with CAP will develop severe disease, as defined by admission to an intensive care unit due to shock or respiratory failure. Approximately one third of patients who develop severe pneumonia have no prior history of significant comorbidities. Determining the severity of illness at presentation is important for prognosis and clinical decision making; assessing whether patients need to be hospitalized or can be managed at home, whether they can be assigned to a general medical bed or require close physiological monitoring in the setting of an ICU. Two tools for assessing severity of illness have proven useful: the CURB-65 and **pneumonia severity index (PSI)**. In addition to pre-existing risk factors (listed above), these tools have identified confusion, uremia, respiratory rate greater than thirty per minute, hypotension (SBP < 90 or DBP < 60), hypothermia (< 35 C) or hyperpyrexia (>40 C) as poor prognostic indicators. Both of these indices have been validated and recom-

mended by the IDSA/ATS community-acquired pneumonia guidelines. The relative disadvantages of these indices include risk factors not included in the CURB-65 criteria, the time-occupying and cumbersome nature of the PSI, and the fact that they may be either redundant or inferior to the clinical judgment of the physician.

Two tools for assessing severity of illness have proven useful: the CURB-65 and pneumonia severity index (PSI).

TREATMENT OF CAP

Multiple studies have demonstrated that a limited number of micro-organisms are responsible for the majority of CAP. From what is known of the likely antibiotic sensitivities of these pathogens, recommendations have been formulated for antibiotic choices before the results of culture and sensitivity studies are known. The most widely used guidelines are those issued by the joint committee of the Infectious Diseases Society of America and the American Thoracic Society¹³. They recommend that empiric treatment of pneumonia in the outpatient setting in a patient who is overall healthy and has no risk factors for antibiotic-resistant pathogens can be treated with either:

Macrolide

- Azithromycin 500 mg orally once, then 250 mg orally daily for the following 4 days

- Clarithromycin 500 mg orally twice daily
- Erythromycin 500 mg orally three times daily; or
- Doxycycline
- 100 mg orally twice daily

For patients with risk factors such as chronic, liver, heart, lung, or kidney disease, diabetes, alcohol usage, asplenia, immunosuppression, any antibiotics in the preceding 3 months, or other risk factors for drug-resistant *S. pneumoniae* (DRSP) including a community-wide prevalence above 25%,

- Beta-lactam plus a macrolide (or doxycycline)
- Amoxicillin 1 gram orally three times daily
- Cefpodoxime 400 mg orally twice daily
- Cefuroxime axetil 500 mg orally twice daily

The outpatient with pneumonia should be encouraged to contact the treating physician or an emergency room if severe dyspnea or worsening clinical status develops. Reassessment of clinical status either by the patient or a health care provider should occur at 48-72 hours to assess for an appropriate response to antibiotics.

For patients warranting admission to the hospital, monotherapy with azithromycin or doxycycline is **not** recommended due to varying prevalence of antibiotic resistance. Non-ICU patients can be treated with either:

- A fluoroquinolone alone for 7-10 days, such as
Levofloxacin 750mg, IV/PO q 24h
Moxifloxacin 400mg IV/PO q 24h
- Or Beta-lactam, such as
Ceftriaxone, 1 g IV q 24h
Cefotaxime, 1g IV q 8h
- Plus, either Azithromycin, Clarithromycin, or Doxycycline

Development of a worsening clinical exam should prompt repeat radiographic examination. An assessment for an adequate response should occur at 48-72 hours of antibiotic administration. Persistent fever should prompt investigation for bacteremic pneumonia including repeating blood cultures.

Most patients with CAP who necessitate admission to an **intensive care unit (ICU)** either have a tenuous or failing respiratory status. The logic behind expanding coverage in patients with similar risk factors to more stable patients reflects the severity of the consequences of leaving the pathogen inadequately covered by the antibiotics chosen. Combination therapy is indicated for these patients. The following are recommended in the guidelines:

- Beta-lactam plus a macrolide or a flouroquinolone
e.g. Ampicillin/Sulbactam, Ceftriaxone, Cefotaxime, Ertapenem
- PLUS Azithromycin, Levofloxacin, or Ciprofloxacin
- For penicillin-allergic patients, Aztreonam plus Levofloxacin or Moxifloxacin is recommended.
- Coverage of MRSA with either Vancomycin or Linezolid should be considered
- If *Pseudomonas* is a suspected pathogen, Piperacillin/tazobactam, Imipenem, Meropenem, or Doripenem should be the beta-lactams used and these should be combined with either Levofloxacin or Ciprofloxacin (400mg IV q8h.)
- Aminoglycoside usage can be considered

Risk factors for MRSA infection should be considered, such as prior colonization, current colonization, home wound care, hemodialysis, and close contacts with an individual with MRSA. Linezolid or vancomycin should be empirically added to the above regimens when suspected. MRSA pneumonias more commonly cause necrotizing infections and empyemas than other pneumonic pathogens.

DE-ESCALATION AND DURATION OF ANTIBIOTIC TREATMENT

Concern for the rising costs of treatment and the rise of antibiotic resistant strains has focused optimizing the duration of intravenous antibiotic use. Conversion from intravenous to oral antibiotics should occur in patients with stable hemodynamics (Temperature 38C or less, pulse ox >92% and respiratory rate 24 or less) who are able swallow and absorb oral medications.

Duration of therapy is usually 5-7 days. A full two weeks rarely needs to be given for community-acquired pneumonia, except for CAP due to atypical organisms such as *Mycoplasma*, *Chlamydia* and *Legionella* species. When a patient shows no or little sign of clinical instability and a clear trend toward improvement, a consideration for stopping antibiotics should occur.

PREVENTION

Prevention of CAP in adults includes vaccinating appropriate groups annually for Influenza and the polysaccharide pneumococcal vaccine. Asplenic patients should be given pneumococcal and the *Haemophilus influenzae* type B vaccines, which may prevent bacteremic pneumonias in this group. Patients admitted to a hospital should be assessed for vaccination status at admission and vaccinated at time of discharge. Encouraging reduction and cessation of smoking in the general and high-risk populations likely will reduce incidence and severities of pneumonia.

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