Community-Acquired Pneumonia: A Focused Review

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Abstract Community-acquired pneumonia (CAP) is a common cause for admission to the hospital and contributes significantly to patient morbidity and healthcare cost. We present a review of the epidemiology, pathophysiology, risk factors, symptoms, diagnosis, presentations, risk-stratification, markers, and management of CAP in the United States (US). The overall incidence of CAP is 16 to 23 cases per 1000 persons per year, and the rate increases with age. Some of the risk factors for CAP include comorbidities such as, chronic obstructive pulmonary disease (COPD), asthma, and heart failure. CAP symptoms vary, and typically include productive cough, dyspnea, pleuritic pain, abnormal vital signs (e.g., fever, tachycardia), and abnormal lung examination findings. A diagnosis can be made by radiography, which has the additional benefit of helping to identify patterns associated with typical and atypical CAP. There are risk-stratification calculators that can be used routinely by physicians to triage patients, and to determine adequate management. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) developed the Pneumonia Severity Index (PSI) which incorporates 20 risk factors to place patients into 5 classes correlated with mortality risk. In addition, the British Thoracic Society (BTS) established the original severity score CURB (confusion, uremia, respiratory rate, low blood pressure) to identify patients with CAP who may be candidates for outpatient vs. inpatient treatment. Inflammatory markers, such as procalcitonin (PCT), can be used to guide management throughout hospital stay. Antibiotic coverage will vary depending on whether outpatient vs. inpatient management is required.

Keywords: Community-acquired pneumonia (CAP), atypical pneumonia, typical pneumonia, procalcitonin, pneumonia severity index, CURB


1. Introduction

CAP is one of the most common reasons for hospitalization in the US. It can affect individuals of any age and cause significant strain on the healthcare system due to its financial burden; but more importantly, it carries significant morbidity and mortality. Most of the mortality occurs in patients that require hospitalization. [1] The understanding of the multiple components about CAP, such as the incidence, epidemiology, and outcomes of patients, can help us guide preventative measures and treatments. [1] The rationale behind this literature review, in addition to what was stated prior, is to point out the benefits of adequate risk-stratification in guiding appropriate management, and some of the clinical benefits of using Procalcitonin as a biomarker for pneumonia. Procalcitonin has been shown to be a promising inflammatory biomarker, with the ability to monitor a patient's response to treatment. The literature seems to favor procalcitonin as being more effective than other inflammatory markers, such as CRP, in terms of guiding appropriate therapy. [2] However, procalcitonin can also be increased in noninfectious diseases, which stresses the importance of follow-up measurements, because procalcitonin levels will be gradually increase in patients with CAP during a follow-up.9 With proper risk-stratification techniques, such as CURB and PSI, we can estimate the risk of mortality for patients. Therefore, risk-stratification can help to triage the appropriate level of care a patient requires, and help to identify those that may have a higher morbidity and mortality from CAP. [3] The pathophysiologic processes of CAP in the human body are well-studied, and as a result we have developed many effective antimicrobial agents to eliminate infection. Empirical treatment is preferred in the management of CAP; however, this is not without risks, such as: allergies, antibiotic-resistance, and antibiotic-misuse. Physicians must be aware that CAP can have a viral etiology in 25% of cases, which may account for poor response to antibiotics or atypical features. [4] The prompt identification and recognition of a viral-CAP, especially during influenza season, can dramatically improve outcomes and reduce mortality. [4]

2. Epidemiology

CAP is the leading cause of infectious disease-related death in the US, with mortality occurring largely in
patients who require hospitalizations. It accounts for 4.5 million outpatient and emergency room visits annually. It is the second most common cause of hospitalizations and the most common infectious cause of death. [5,6] It is estimated that 1.5 million unique CAP hospitalizations occur each year. CAP is not a reportable infection in the United States; therefore, data regarding the burden of the disease is primarily obtained through clinical investigation. [1] The University of Louisville Pneumonia Study was a prospective population-based cohort study of all hospitalized adults with CAP who resided in Louisville, Kentucky between 2014-2016. The patients in the study were defined as having CAP when 3 criteria were met: (1) presence of a new pulmonary infiltrate on chest radiograph and/or chest CT scan at time of hospitalization; (2) at least one of the following: (a) new cough or sputum production, (b) fever > 37.8°C, or hypothermia < 35.6°C, (c) changes in leukocyte count (leukocytosis > 11,000 cells/µL; left shift >10% band forms/mL; or leukopenia: <4000 cells/µL); and (3) no alternative diagnosis at time of hospital discharge that justified the presence of criteria 1 and 2. During the 2-year study period, a total of 8284 hospitalizations were due to CAP. [1] The study indicated the annual incidence of adult patients hospitalized with CAP in the city of Louisville is 634 per 100,000 adults, the annual incidence of adult patients hospitalized with CAP is 1507 for the age range 65-74, 2205 for 75-84 years of age, and 3951 for greater than 85 years of age. It is estimated that approximately 100,000 adults will die during their hospitalizations due to CAP. Approximately 1 of 10 patients hospitalized with CAP required a second hospitalization due to a new episode of CAP during the same study year. Efforts to advance adequate prevention strategies and treatment modalities are needed. [1]

3. Methods

We performed an extensive search on PubMed, and Cochrane database, looking for studies published most preferably within the last five to ten years. We also performed individual search or references from relevant articles that we came across related to CAP. The University of Louisville Pneumonia Study was the main study we came across that was used to argue the burden of CAP on the population, it was a prospective population-based cohort study which included inpatient patients. A search of relevant reviews for epidemiology, pathophysiology, risk factors, symptoms, diagnosis, presentations, risk-stratification, markers, and management of CAP in the United States was done, and included in the review. A search on PubMed was done for specific dosages for antibiotic management.

4. Pathophysiology

Pneumonia is an alveolar infection that occurs when the immune system is unable to clear a pathogen from the lower airway and alveoli. [4] Immune cells release cytokines and local inflammatory mediators, which cause additional damage to the lung parenchyma. Systemic inflammation ensues, leading to secondary symptoms such as fevers, chills, and fatigue. Accumulation of white blood cells and fluid congestion results in pus in the parenchyma with subsequent decreased compliance of the alveoli. These changes increase the patient’s work-of-breathing and, ultimately, worsens hypoxemia and tachypnea. [8] (Figure 1) Pneumonia can affect patients of all ages and across all spectrums of health. Clinical comorbidities that dampen the mucociliary clearance and cough reflex can increase the chances of acquiring CAP. Social habits such as smoking also put patients at increased risk. Medical conditions that increase the risk of aspiration are also of concern, such as esophageal disorders, alcoholism, and neuromuscular disorders. [4,8,9,10]

5. Risk Factors

Several risk factors for CAP are commonly found in the developed and developing countries, including smoking tobacco, exposure to animals, and recent upper respiratory tract infections (URTI). Smoking is a well-known risk factor for CAP with the risk being much higher for ex-smokers. Passive smoking is not associated with an increased CAP risk in adults, but it is a known risk factor for lower respiratory tract infections (LRTIs) among children. [3] Smoking significantly increases the risk of acquiring CAP among immunocompromised patients such as HIV. [3] Smoking also has a suppressive effect on the protective actions of airway muco-ciliary clearance mechanisms, and on the various components of the innate and adaptive immune systems of the hosts, as well as direct effects on microbial pathogens that promote their virulence. [8,9,10]

Several comorbid factors are well documented in the literature to increase the risk of CAP. One of the most common is chronic obstructive pulmonary disease (COPD). [8,9,11] In older individuals, asthma can be a significant risk factor for CAP. Inflammation, bronchial obstruction, and hyperresponsiveness associated with asthma favors microorganism colonization. The evidence regarding the effects of other respiratory diseases such as bronchiectasis, pulmonary fibrosis, and tuberculosis is insufficient. There may be some association between the medications used for the respiratory diseases and the development of CAP, independent of the underlying respiratory illness. Some randomized controlled trials have shown an association between corticosteroids and the development of a lung infection as a side effect, especially in patients with COPD. [9] (Table 1)

Furthermore, other comorbid conditions increasing the risk of developing CAP include congestive cardiac failure, diabetes mellitus, alcoholism, hepatic, renal insufficiency, and malignancy. Interestingly, recent studies have identified several mechanisms, specifically the presence of
certain gene polymorphisms which contribute to an increased susceptibility for development of CAP, as well as a worse disease outcome. [12] These include single nucleotide polymorphisms (SNPs) in genes encoding proteins of the immune system. For example, IL-6 174G/G has been reported to protect patients with pneumococcal CAP against the development of ARDS, septic shock, and multiple organ dysfunction syndrome, which results in lower mortality. [3] In addition, there is ongoing investigation of the role of SNPs in the genes encoding the surfactant proteins (SP) A, B, C, and D, which revealed associations with susceptibility for the development of CAP and susceptibility for a more severe disease course. [1,9]

Figure 1. Schematic description of the pathophysiology of pneumonia
RISK FACTORS

It is well known that age is a significant risk factor, especially among the very old (>84 years), in part due to waning immunity. Notably, the incidence of CAP increases 5-fold with age from 8.4 per 1,000 in those aged 65-69 years to 48.5 per 1,000 in those at least 90 years old. Although age by itself is not associated with a worse prognosis in the elderly hospitalized with CAP, a fatal event after CAP is often more probable in persons over the age of 65 years. In a retrospective analysis of older patients with CAP, mortality during the first 30 days was 20.7% in the older and 11.9% in the younger group (p<0.001). Additional research has observed that individuals over the age of 65 years of age had a higher 1-year mortality rate after being hospitalized for CAP compared with case-matched controls. [13] They observed that nearly half of all elderly patients admitted for CAP died in the subsequent year, with most of the deaths occurring after hospital discharge. However, advanced age is not an independent risk factor for a poorer prognosis. [1,14]

Of note, male gender has been identified as having a greater incidence of CAP and a worse prognosis. [3] Males were more likely to be admitted to the ICU, and more likely to die, compared with their female counterparts. [13] It is not completely understood why this relationship exists, but there is literature suggesting that in both animal and human models women are less likely to develop sepsis secondary to CAP, and are, therefore, less likely to succumb to this infection. Cell-mediated immunity is depressed in males compared to females, and that the higher estradiol levels in females may offer enhanced protection. [1,9,15]

6. Risk-Stratification

The pneumonia assessment systems, such as PSI and CURB, were designed to direct the appropriate level of care, based on a 30-day mortality risk. These tools are used to guide appropriate empirical antibiotic treatment, and occasionally, identify patients who will require admission to the ICU. PSI, also known as the Fine score, classifies patients with CAP into five classes based on their risk of death within 30 days. [3] The score is based on 20 clinical, laboratory, and radiographic variables from data validated on more than 40,000 inpatients. [12,14,16]

Pneumonia Severity Index (PSI): [3]
- Class I is determined by absence of the following risk factors:
  - Age > 50 or temperature > 40°C
- Class II - V is determined by a patient’s total risk score, which in addition to the risk factors above, includes demographic factors (male sex and nursing home residence) and seven laboratory or radiographic findings:
  - BUN concentration >30 mg/dL
  - Glucose concentration >250 mg/dL
  - Hematocrit <30%
  - Sodium concentration <130 mmol/L
  - Partial pressure of oxygen <60 mmHg
  - Arterial pH <7.35
  - Pleural effusion
- Class IV/V suggests severe/life-threatening CAP.

CURB: The British Thoracic Society (BTS) established the original CURB to identify patients with CAP who may be candidates for outpatient vs. inpatient treatment. [3] The difference between CURB and PSI is that the former does not directly address underlying disease. The criteria for CURB include:
- Respiratory rate > 30/min
- Diastolic blood pressure <60 mmHg
- Elevated BUN >20 mg/dL

These criteria are reliable, except in patients with underlying renal insufficiency and in the elderly. A multivariate analysis of 1,068 patients allowed for the development of the modified six-point CURB-65 score, which includes the same criteria as above plus the additional criteria of Age > 65 years. A score of at least 3 indicates ICU care. The CURB scoring system tends to be favored over the PSI method because it directly measures the severity of CAP vs. the risk of mortality. [3]

7. Symptoms

CAP is an infection of the lungs that results in inflammation and abnormal function. [11] There are slight differences in symptoms at presentation between typical and atypical pneumonia. Clinical manifestations include findings due to damage to the lung and related tissue. Significant findings in the history include:
- Fever
- Tachycardia
- Chills & sweats
- Cough with productive/non-productive sputum or blood-tinged
- Pleuritic chest pain
- Shortness of breath
- Headaches, fatigue, and myalgia

Sputum production tends to be the most significant pulmonary manifestation in typical pneumonia. [4] There also seems to be an association with certain sputum production with a specific causative organism:
- Rust-colored sputum - S. pneumoniae
- Green sputum - P. aeruginosa
- Red currant-jelly sputum - K. pneumoniae
- Foul-smelling sputum - Anaerobes
8. Etiology

Microbiological diagnosis of CAP is important because it guides antimicrobial guidance. However, microbial diagnosis of pneumonia is achieved in less than 50% of cases and antimicrobial therapy is typically given empirically in order to avoid delay in management initiation. [6] Of note, bacteria tend to be detected as the more frequent culprit of CAP, in comparison with viruses or fungi. [8]

*S. pneumoniae*: Traditionally the most common cause of CAP, it presents with acute symptoms of lower respiratory tract infection, fever, and rust-colored sputum. [8] The incidence of pneumococcal pneumonia has decreased due to the introduction and wide usage of pneumococcal vaccines. The diagnosis of pneumococcal pneumonia has increased in recent years, partly due to the introduction of a pneumococcal urine antigen test. [8] The polysaccharide capsule is one of the most important virulence factors, and it has different chemical and antigenic compositions that result in 93 different pathogenic serotypes. Some of the more common serotypes include 6A, 6B, 9V, 14, 19A, 19F and 23F. [8]

*H. influenzae* is a frequent pathogen of CAP, it has been the causative agent in 1.8% - 8.3% of CAP that required ICU admissions. [8,21] In these cases, there was a case-fatality rate of 50% - 100%. A recent study found that about 1% of the cases were caused by a multidrug-resistant (MDR) P. aeruginosa. [21] Infection with this organism tends to have poorer clinical outcomes and must include special antibiotic coverage, as the empiric regimen does not typically offer pseudomonas coverage. A large proportion of patients hospitalized with *P. aeruginosa* do not have risk factors for the infection at presentation, and the empirical use of antipseudomonal antimicrobial therapy can lead to a better survival for patients with CAP. [21]

*Legionella pneumophila*: Legionnaires disease (LD) is caused by the gram-negative bacilli *L. pneumophila*, which results in a pneumonic illness. It is classified as an “atypical pneumonia” because it presents with different symptomatology, an interstitial pattern on x-ray and responds to different antibiotics than pneumonia caused by typical bacteria (e.g., *S. pneumoniae*, *H. influenzae*, *S. aureus*). However, a recent study found that LD presents with atypical radiographic features. They argue that the accumulated evidence that clinical features are of limited utility in identifying the offending pathogens, and that their results support the notion that LD has nothing “atypical” in its radiological manifestation. Furthermore, the study suggests that atypical pneumonia should only refer to lower respiratory tract infections caused by specific respiratory pathogens including *C. psittaci* (psittacosis), *F. tularensis* (tularemia), *C. burnetii* (Q fever), *C. pneumoniae*, *M. pneumoniae*, or *Legionella* species regardless of the clinical or radiological manifestations. [17] The study sheds new light on the common belief that LD presents with atypical radiographic features. [21]
can still be made by culture, serological investigation, or urinary antigen detection. [17]

Haemophilus influenzae: A gram-negative, oxidase positive rod that is a facultative anaerobic and nonmotile. It is primarily spread from person-to-person via airborne droplets or through direct contact with respiratory secretions from infected or colonized individuals. [11] The nasopharynx is the most common site of colonization. The outer membrane of H. influenzae contains several adhesins that mediate attachment to the respiratory tract epithelium including pili, fimbiae, and high molecular weight factors (HMW1 and HMW2). [11] The innate and acquired humoral immunity play important roles in host defenses. One of the most important structural defenses is the mucociliary apparatus, which can be paralyzed with exposure to cigarette smoke. [3,11] Additionally, H. influenzae’s lipo-oligosaccharide activates the alternative complement pathway, which stimulates the C3b opsonization and subsequent bacterial phagocytosis. [11] Individuals with complement deficiency were at increased risk for H. influenzae infections. [11] Current empiric management will treat H. influenzae, which include amoxicillin, amoxicillin-clavulananate, or second and third generation cephalosporins, fluoroquinolones, macrolides, and tetracyclines. [11]

Mycoplasma pneumonia: This pathogen can produce mild URTI and atypical pneumonia. Additionally, it can produce a wide array of non-pulmonary manifestations which include neurological, hepatic, cardiac disease, anemia, polyarthritis and erythema multiforme. [22] Mycoplasmas can be differentiated from other bacteria by their lack of cell wall, which makes the organisms insensitive to beta-lactam antimicrobial agents and unable to be stained with gram’s stain. Infection course usually begins with pharyngitis followed by hoarseness, fever, and chills. The cough is initially non-productive but can progress to production of moderate amounts of non-bloody sputum. Macrolides or tetracyclines are the cornerstone of treatment. [22]

Viruses: Viruses are considered to be the etiological agent in almost one-third of cases of CAP, the most common of which include influenza viruses (A and B), rhinoviruses, parainfluenza viruses 1, 2, and 3, and coronaviruses. It is estimated that 100 million cases of viral pneumonia occur globally each year. [8] The majority of deaths correspond to patients with underlying risk factors, such as metabolic syndrome and immunosuppression. [8] Respiratory syncytial virus (RSV) has also been identified as an important cause of pneumonia in adults in the last 20 years. [8] It is the second most common cause of viral pneumonia in the elderly. Overall, RSV has an etiology of CAP between 2% and 5% throughout the year. Immunosuppression as well as other transient immunosuppressive states are significant risk factors for RSV infection. [5] (Table 2)

9. Diagnosis

CAP can be defined both on clinical and radiographic findings. Clinically, CAP is characterized by:

- Symptoms of an acute lower respiratory tract illness (cough with or without expectoration, shortness of breath, pleuritic chest pain) for less than 1 week
- At least one systemic feature (temperature > 37.7°C, chills, and rigors, and/or severe malaise)
- New focal chest signs on examination (bronchial breath sounds and/or crackles), with no other explanation for the illness

If imaging is available, CAP can be defined as the clinical presentation described above along with new radiographic shadowing for which there is no other explanation. [8] Findings in the radiographic image may be a lobar or patchy consolidation, loss of a normal diaphragmatic, cardiac or mediastinal silhouette, interstitial infiltrates or bilateral perihilar opacities, with no other obvious cause. [8,11,17]

A complete blood count with serum electrolytes, renal and liver function tests can also be helpful in the diagnosis of CAP patients. If patients are hospitalized, blood and sputum cultures should be collected, preferably before the initiation of antibacterial medications. Urine antigen tests can be performed, especially if Legionella is suspected. PCT has been used as a biomarker for antimicrobial therapy guidance since it can be elevated in bacterial infections. During the winter seasons, an influenza test is also recommended. This is because a superimposed bacterial infection can occur after a viral infection. If available, testing for respiratory viruses on nasopharyngeal swabs by molecular methods can be considered.

10. Procalcitonin

Procalcitonin remains one of the most widely used biomarkers for pneumonia. During a bacterial infection, the CALC-1 gene is upregulated which results in the increased production of procalcitonin by innate immune cells such as macrophages. [2,23] The increase in production of procalcitonin tends to occur in the liver, lung, and intestines. Procalcitonin is identifiable within 2-3 hours, with a peak at 6 hours. Procalcitonin seems to have an advantage over c-reactive protein (CRP) because of its earlier increase with infection onset. [2,23] It also has a better negative predictive value, which has been observed in children with fever of unknown origin or adults in the ICU with sepsis. [2,23] Procalcitonin can reduce antibiotic usage by reducing the duration of an antibiotic course. [23] It is important to note that persistent elevated procalcitonin levels may indicate a complicated course, but there is also the possibility that it could be falsely elevated. In contrast, persistent low levels of procalcitonin can be seen in localized infections (e.g., empyema, abscess). In bacterial CAP, a delay in the initiation of antibiotic therapy can be associated with an increased mortality. If a patient presents with an infiltrate on chest radiograph in the presence of acute respiratory symptoms and repetitively low procalcitonin levels, physicians should consider other diagnosis than bacterial pneumonia such as: viral pneumonia, pulmonary embolism, congestive heart failure, and others. In contrast, procalcitonin levels that are >0.25 µg/L - 0.5µg/L support the diagnosis of CAP. [2]

11. Management

Antibiotic therapy is initiated on an empiric basis since the causative organism is rarely identified in the majority
of disease. Recommendations for the treatment of hospitalized patients vary based on the required level of care. Most patients that present to the hospital are started on intravenous (IV) therapy and then transitioned to oral therapy as their condition improves. For patients admitted to the general ward without a suspicion of *Pseudomonas* or other multi-drug resistant pathogen, the following medications are suggested:

- **Ceftriaxone (1-2 g IV daily) plus macrolide (Azithromycin [500 mg IV or orally daily] or Clarithromycin [500 mg twice daily] or Clarithromycin XL [two 500 mg tablets once daily])** [4,5]
- **Cefotaxime (1-2 g IV every 8 hours) plus macrolide (Azithromycin [500 mg IV or orally daily] or Clarithromycin [500 mg twice daily] or Clarithromycin XL [two 500 mg tablets once daily])** [4]
- **Ceftaroline (600 mg IV every 12 hours) plus macrolide (Azithromycin [500 mg IV or orally daily] or Clarithromycin [500 mg twice daily] or Clarithromycin XL [two 500 mg tablets once daily])** [24]
- **Ertapenem (1 g IV daily) plus macrolide (Azithromycin [500 mg IV or orally daily] or Clarithromycin [500 mg twice daily] or Clarithromycin XL [two 500 mg tablets once daily])** [24]
- **Ampicillin-sulbactam (3 g IV every 6 hours) plus macrolide (Azithromycin [500 mg IV or orally daily] or Clarithromycin [500 mg twice daily] or Clarithromycin XL [two 500 mg tablets once daily])** [4,24]
- **Respiratory fluoroquinolone (Levofloxacin [750 mg IV or orally daily] or Moxifloxacin [400 mg IV or orally daily] or Gemifloxacin [320 mg orally daily])** [4,24]

Doxycycline may be used as an alternative to a macrolide. In addition, treatment with respiratory fluoroquinolones are appropriate for patients who cannot tolerate a beta-lactam plus a macrolide.

For patients admitted to the ICU, empiric management must include an anti-pneumococcal beta-lactam plus IV azithromycin or a fluoroquinolone. [5] Coverage can be expanded to include gram-negative pathogens, such as beta-lactamase-producing *H. influenzae* and *M. catarrhalis*. [4,5] Vancomycin or linezolid can be added if MRSA risk factors exist. For atypical pathogens, a macrolide or doxycycline can be added in addition to beta-lactams. [4,5]

In the outpatient setting, empiric treatment that covers the most common bacterial causes of CAP are used. These include beta-lactams, amoxicillin and amoxicillin-clavulanate can be used for outpatient treatment. [4,5]

12. Conclusion

CAP is the leading cause of infectious disease-related deaths in the United States, and the second most common cause of hospitalizations. [5,6] It can affect patients of all ages and across all spectrums of health, with most of the hospitalizations occurring in older patients. [8,9] Clinical manifestations can range based on the etiology of CAP, but sputum production tends to be the most significant manifestation in typical pneumonia. [4] Recent studies have shown that Legionnaires disease can have similar radiographic and tomographic manifestations that are similar to those found in typical CAP, and the proper diagnosis of Legionnaires disease rests upon the laboratory-based diagnostic tests plus the clinical and radiological diagnosis of pneumonia. [17] The management of CAP tends to be empirical antibiotic treatment, which can present with risks. However, with proper risk-stratification techniques, such as CURB and PSI, we can better guide antibiotic treatment. [14,16] We hope that through this literature review, we have spread awareness about the prevalence of CAP and the utility of risk stratification methods, using procalcitonin as a biomarker and the many considerations to be aware of in terms of antibiotic therapy initiation.

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References


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