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Review article

Severe community-acquired pneumonia

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Abbreviations

ATS	– American Thoracic Society
BUN	– blood urea nitrogen
CAP	– community-acquired pneumonia
ICU	– intensive care unit
IDSA	– Infectious Diseases Society of America
MRSA	– methicillin-resistant *Staphylococcus aureus*
PCR	– polymerase chain reaction
PaO2/FiO2	– the ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration
SARS-CoV-2	– Severe acute respiratory syndrome coronavirus 2

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Abstract

Background and purpose: *Community-acquired pneumonia (CAP) represents a major global health concern due to its high morbidity and mortality. Severe community-acquired pneumonia (sCAP) is characterized by respiratory failure requiring invasive mechanical ventilation and/or septic shock. This narrative review outlines current diagnostic and therapeutic strategies for sCAP.*

Materials and methods: *A review of the bibliographic database PubMed was made.*

Results: *The primary bacterial pathogens include* Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Mycoplasma pneumoniae, *and* Legionella pneumophila. *In recent years, respiratory viruses, particularly influenza and SARS-CoV-2, have become increasingly recognized as significant etiological agents. This narrative review outlines current diagnostic and therapeutic strategies for sCAP. Diagnostic evaluation for hospitalized patients typically includes blood cultures, sputum Gram stain and culture, urinary antigen testing for* S. Pneumoniae *and* Legionella*, and screening for respiratory viruses. Multiplex polymerase chain reaction (PCR) assays capable of detecting a wide range of viral and bacterial pathogens are increasingly used. Management of sCAP involves immediate empirical antibiotic therapy, typically combining a β-lactam with a macrolide or a fluoroquinolone. Adjunctive therapies such as corticosteroids and antiviral medications may be considered in specific cases. Despite therapeutic advancements, sCAP remains associated with high mortality rates, reaching up to 35% in intensive care unit patients. Preventive measures including pneumococcal and influenza vaccination, smoking cessation, and timely medical intervention play a crucial role in reducing disease burden.*

Conclusions: *Continued research and clinical innovation are essential to improving outcomes and minimizing the global impact of sCAP.*

INTRODUCTION

Community-acquired pneumonia (CAP) refers to an acute infection affecting the lung parenchyma that develops outside of a hospital setting. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) define severe community-acquired pneumonia (sCAP) as requiring admission to the intensive care unit, particularly when patients need either mechanical ventilation or vasopressor support due to septic shock. These two conditions represent the major criteria for sCAP. To help identify patients at risk of organ failure early, the IDSA/ATS guidelines also advise ICU admission when a patient presents with at least three of nine minor criteria. These include confusion, low blood pressure requiring fluid resuscitation, hypothermia

(temperature below 36°C), elevated respiratory rate (≥30 breaths per minute), a PaO_2/FiO_2 ratio of 250 or less, blood urea nitrogen levels of 20 mg/dL (7 mmol/L) or higher, a white blood cell count below 4,000/μL, platelet count under 100,000/μL, or evidence of multilobar lung infiltrates *(1).*

CAP represents a significant public health concern. Its incidence rates differ across regions, with estimates in Europe ranging between 1.07 and 1.2 cases per 1,000 person-years. The likelihood of developing pneumonia rises notably with age. Among individuals aged 65 and older, the incidence reaches approximately 14 cases per 1,000 person-years *(2).* In the United States, the overall incidence is estimated at 24.8 cases per 10,000 adults annually, with a marked increase observed in older populations *(3).* Several studies have reported an increase incidence of pneumonia in recent decades *(4,5).* This is partly explained by the higher proportion of patients with an increased risk of respiratory infections due to comorbidities, various immunosuppressive conditions, unhealthy lifestyles and by an aging population. Older age is associated with increased CAP morbidity and mortality. This is explained by age-linked immune dysfunctions and the greater presence of chronic diseases *(6).* Pneumonia ranks as the eighth most common cause of death overall and holds the top position among fatalities caused by infectious diseases. For patients who require the ICU, the mortality rate remain as high as 27-35% *(7,8).* Even those patients who survive to hospital discharge have a higher long-term mortality rate. Close to 50% of individuals admitted to the ICU for treatment do not survive beyond one year *(7).*

ETIOLOGY

CAP can be caused by a wide range of pathogens, including bacteria, viruses, and occasionally fungi. Earlier prospective studies investigating the causes of CAP in adults were unable to determine a specific causative agent in over 60% of cases *(8).* With the introduction of multiplex polymerase chain reaction (PCR) tests in real time, the percentage of positive tests has increased significantly. In a study of hospitalized patients with CAP conducted in Sweden, using a combination of PCR and cultures, the etiology was determined in 68 percent of patients *(9),* while in a study conducted in the United Kingdom, the causative agent was identified in as many as 87 percent of cases *(10).* The most frequently identified cause of pneumonia worldwide is *Streptococcus pneumoniae*, but recently the role of viruses in the etiology of CAP has become increasingly clear *(10).* In a prospective study of 518 hospitalized patients with CAP, bacteria were identified in 55 percent of patients, viruses in 28 percent, and simultaneous viruses and bacteria in 15 percent of patients. *Streptococcus pneumoniae* has been identified in approximately one-third of CAP cases, with Haemophilus influenzae detected in 17%, Moraxella catarrhalis in 9%, and Mycoplasma pneumoniae in 6% *(9).* In one study involving 323 adults treated for CAP in a hospital setting, H. influenzae was found in 40.5% of cases, S. pneumoniae in 30%, and respiratory viruses in another 30%. Notably, 82% of virus-positive samples also tested positive for bacterial pathogens, emphasizing the significance of viral-bacterial coinfections *(10).* Pathogen distribution has been shown to vary with disease severity *(10,11).* For instance, in a cohort of 3,523 CAP patients at Hospital Clinic in Barcelona, a causative agent was identified in 42% of cases. The prevalence of certain pathogens differed by level of care, with S. pneumoniae and mixed infections becoming more frequent in hospitalized and ICU patients, while atypical pathogens were less common *(11).* Among patients admitted to ICU, S. pneumoniae remained the most commonly isolated organism, followed by Legionella, *gram-negative bacilli*, Staphylococcus aureus, and influenza virus *(10).*

The *S. pneumoniae* incidence varies worldwide. In the United States, is estimated that *S. pneumoniae* is responsible for 20 percent of CAP cases *(12).* In Europe this percentage is higher, and according to some studies reaches 36 percent *(10).* This finding is likely related to differences in vaccination practices and smoking habits. Children under the age of two and older adults are particularly vulnerable to developing pneumococcal pneumonia. Viral infections, notably influenza and SARS-CoV-2, can predispose individuals to secondary pneumococcal infections. Other risk factors include chronic lung diseases, immunosuppression, splenectomy, alcoholism, smoking. In Croatia, resistance of *S. pneumoniae* to penicillin is low. In 2021, 4% of penicillin-resistant strains were registered, and 16% were susceptible at increased exposure. In order to effectively treat *S. pneumonia* that are susceptible at increased exposure, empiric

Table 1. *Common causes of community-acquired pneumonia (CAP) (1)*

Bacterial Pathogens
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Atypical Pathogens
Chlamydophila pneumoniae
Mycoplasma pneumoniae
Legionella pneumophila
Viral Pathogens
Influenza virus A and B
Respiratory syncytial virus (RSV)
Adenovirus
Human metapneumovirus

treatment of pneumonia should be started with higher doses of penicillin *(13).* Risk factors for drug-resistant S. pneumoniae are listed in Table 2. Resistance of pneumococci to macrolides is high in Croatia. In 2021, 28% of strains were resistant to macrolides *(13).* Therefore, monotherapeutic use of macrolides should be limited only to the treatment of atypical pneumonia in patients with a mild form of the disease *(14).* Common causes of CAP are listed in Table 1.

Legionella pneumophila is responsible for approximately 3–6% of hospital-treated CAP cases *(17).* Of the more than 15 identified serogroups, serogroup 1 is the most frequently encountered *(18).* Transmission does not occur from person to person; instead, infection arises through inhalation of aerosolized particles from contaminated water or soil. Individuals at increased risk include older adults, smokers, those with chronic lung conditions, and people with compromised immune systems. Clinical features suggestive of *Legionella pneumonia* include high fever, hyponatremia, high serum lactate dehydrogenase levels, neurological symptoms such as confusion, and impaired cognition may occur *(19). Legionella* can cause severe disease, with a mortality rate of 5-25% *(17).*

Gram-negative bacilli play a significant role in patients with severe pneumonia admitted to the ICU. Key pathogens in this group include Klebsiella pneumoniae, Escherichia coli, species of Enterobacter, Serratia, Proteus, and Pseudomonas aeruginosa. In people with significant comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, alcoholism, Klebsiella *pneumoniae* should be considered as the causative agent of the disease (20). Risk factors for *Pseudomonas aeruginosis* include hospitalization and/or intravenous antibiotic use within the prior three months, previous colonization or infection with the same pathogen, structural lung diseases (such as COPD, bronchiectasis, pulmonary fibrosis), immunosuppression, presence of multiple medical comorbidities (Table 2) *(21).*

S. aureus pneumonia is characterized by necrotizing or cavitary pneumonia, empyema may often be present. It most often occurs as part of staphylococcal sepsis. It can be expected in the elderly and has high morbidity and mortality *(22).* Risk factors for methicillin-resistant *Staphylococcus aureus (MRSA)* include previously known *MRSA* colonization or infection, hospitalization and/or use of antibiotics in the last three months, severe renal failure, living in a collective, intravenous drug use (Table 2) (23).

In recent times, viral agents like influenza and SARS-CoV-2 have become increasingly important, especially during seasonal epidemics and global pandemics. Influenza remains the leading viral cause of CAP. Other notable respiratory viruses include respiratory syncytial virus, parainfluenza viruses, adenoviruses, rhinoviruses, coronaviruses, and human metapneumovirus *(24).* Also, mixed viral-bacterial infections are common. It is believed that viral infection impairs the local defense of the airways and predisposes lower respiratory tract bacterial superinfection. Mixed infection is associated with a more severe form of CAP and the need for longer hospitalization *(25).* Influenza can cause primary influenza pneumonia or, more commonly, predispose the respiratory system to bacterial superinfection. The primary bacterial pathogens responsible for secondary pneumonia include Streptococcus pneumoniae, Staphylococcus aureus, and Group A *Streptococci*. The pathophysiology of sCAP involves the inhalation or aspiration of these microorganisms, triggering an intense inflammatory response in the lungs. This

Table 2. *Risk factors for specific types of bacteria (1,16,17,21,23)*

Bacteria	Risk factors
Drug-resistant *S. pneumoniae*	Age over 65 years Use of beta-lactam, macrolide, or fluoroquinolone antibiotics within the last three months Presence of medical comorbidities such as asthma, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, sickle cell disease, or liver and kidney disorders Alcohol abuse Immunosuppressive illness or therapy
Pseudomonas aeruginosa	Known colonization or past infection Hospitalization with receipt of intravenous antibiotics within the prior three months Pulmonary comorbidities, such as cystic fibrosis, bronchiectasis, or frequent exacerbations of chronic obstructive pulmonary disease (COPD) Multiple medical comorbidities (eg, diabetes mellitus, alcoholism) Immunosuppression
Methicillin-resistant Staphylococcus aureus	MRSA colonization or past infection with MRSA Antibiotic use within the past three months Hospitalization within the past three months End-stage kidney disease Crowded living conditions Recent influenza-like illness

leads to alveolar infiltration, impaired gas exchange, and, in severe cases, acute respiratory distress syndrome (ARDS). The widespread inflammatory reaction can also result in sepsis and multi-organ failure, increasing the risk of death.

MICROBIOLOGICAL TESTING

For patients with CAP requiring hospitalization, comprehensive microbiological evaluation is recommended. Identification of the causative agent has several advantages. It enables the application of targeted antimicrobial therapy. Targeted therapy may reduce the side effects and prevents antimicrobial resistance. The identification of the causative agent enables a change to the appropriate antibiotic, if empiric therapy is not adequate. It also provides insight into the local epidemiological situation, and the need to implement infection control measures.

In patients with sCAP who require ICU admission, microbiological evaluation involves collecting both non-invasive and invasive specimens. This typically includes blood cultures, sputum Gram staining and culture, urinary antigen tests for Streptococcus pneumoniae, assays for Legionella, and viral testing when respiratory viruses are prevalent in the community *(19).*

Ideally, two blood culture sets (aerobic and anaerobic) from separate sites should be taken before antibiotic administration. A positive blood culture confirms the etiological diagnosis of pneumonia. Blood cultures have limited diagnostic sensitivity, yielding positive results in only 4–17% of patients hospitalized with CAP. The likelihood of a positive blood culture tends to increase with the severity of illness. In a study involving over 130,000 pneumonia patients, blood cultures were positive in 4.7% of cases, with Streptococcus pneumoniae being the most frequently isolated bacterium, followed by Staphylococcus aureus and Pseudomonas aeruginosa *(26).*

Sputum is a valuable microbiological material, but has some disadvantages. The sample may be contaminated with oral flora, a large percentage of patients cannot provide an adequate sample or do not cough productively. The adequate sample for analysis must be a deep cough sample. It is recommended to be obtained before the start of antimicrobial therapy, preferably in the presence of a healthcare professional and processed within two hours of collection. Only a sample of appropriate quality should be taken for microbiological processing. The quality of sputum is determined by microscopic examination at low magnification. A sputum sample is considered of adequate quality if there are > 25 neutrophils and < 10 epithelial cells in the field of view *(27).* Given that timely antimicrobial therapy is the key to successful treatment, it should not be delayed if the patient is unable to cough *(19).* In intubated patients, lower respiratory tract specimens should be promptly collected and sent for Gram stain and culture. This is particularly important in order to identify, as soon as possible, the presence of so-called "non-core pathogens" such as *S. auresus MRSA* or *P. aeruginosa*, which will allow treatment to be adjusted *(1).*

Urinary antigen tests are available for detecting Streptococcus pneumoniae and Legionella pneumophila serogroup 1. These tests offer advantages such as ease of use, rapid results within minutes, and the ability to be conducted at the point of care. Their sensitivity is around 70%, and the specificity is over 98% *(28,29).*

PCR testing of nasopharyngeal swabs remains the preferred method for detecting viral infections, especially for influenza and SARS-CoV-2, as effective antiviral treatments are available *(31).* When a virus is identified without any clinical, microbiological, or biochemical evidence of bacterial infection, clinicians are advised to consider reducing or discontinuing antibiotic therapy *(23).* The use of multiplex molecular assays, which can simultaneously detect a broad range of viruses—including influenza A and B, respiratory syncytial virus, parainfluenza, adenovirus, SARS-CoV-2, and human metapneumovirus—is becoming more widespread. Multiplex PCR tests that detect bacterial and viral pathogens are also used. They represent advanced diagnostic tools that allow the simultaneous detection of multiple respiratory pathogens from a single patient sample. By using specific molecular probes that target the DNA or RNA of various viruses and bacteria, these tests provide rapid and accurate identification of infectious agents, which is crucial for timely and appropriate treatment. There are two main types of multiplex PCR panels: respiratory panels and pneumonia panels. Respiratory panels are designed to detect the most common viral and bacterial pathogens responsible for upper and lower respiratory tract infections. These include viruses such as influenza A and B, respiratory syncytial virus, adenovirus, rhinovirus, various coronaviruses (including SARS-CoV-2), and parainfluenza viruses. Bacterial targets may include *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Bordetella pertussis*. These panels are particularly useful for diagnosing the cause of acute respiratory symptoms such as cough, fever, sore throat, and shortness of breath. Pneumonia panels, on the other hand, are tailored to identify pathogens associated with more severe lower respiratory tract infections, especially in hospitalized or immunocompromised patients. These panels typically include bacterial pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae*. They may also provide important clinical value by detecting non-core pathogens, including Staphylococcus aureus *(MRSA),* Pseudomonas species, and multidrug-resistant organisms such as ESBL-producing and carbapenem-resistant Enterobacterales and Acinetobacter species. Early identification of these pathogens can facilitate the prompt initiation of appropriate antibiotic therapy. Some versions also detect respiratory viruses and genetic markers of antibiotic resistance. However,

caution is needed in data interpretation. These tests are very sensitive and the probability of pathogen detection is higher than with standard microbiological methods *(30, 31)*. The detected pathogen could only colonize the respiratory tract and does not have to be the cause of the disease. At the same time, it is necessary to take into consideration that the causative pathogen may not be included in the tested panel.

The precise impact of multiplex molecular assays on the clinical management of CAP remains unclear. In a study that randomly assigned patients with suspected CAP to either rapid multiplex molecular diagnostics or usual care, the use of molecular diagnostics led to increased rates of pathogen-directed therapy by 22 percent. Testing allowed antibiotic escalation in 15 percent of patients and tapering in 10 percent, but clinical outcomes were not significantly different between groups *(32)*.

ANTIBIOTIC THERAPY

Managing sCAP demands a thorough and multifaceted strategy. Initial antibiotic therapy is typically empirical since the exact pathogen is usually unknown at the start of treatment. The selection of antibiotics is guided by the most probable causative organisms, local epidemiological data, clinical presentation, and the patient's individual risk factors and comorbidities. Treatment for sCAP differs from that for milder cases, reflecting the involvement of a broader range of potential pathogens. The success of treatment largely depends on timely antibiotic therapy. Studies have demonstrated that initiating treatment within four hours of hospital admission decreases both mortality rates and length of hospital stay *(33)*. In patients with sCAP, it is recommended to administer the first dose of antibiotics within one hour of admission to the ICU *(14)*.

For patients admitted to the ICU with sCAP, initial antibiotic therapy should consist of beta-lactam combined with either a macrolide or a respiratory fluoroquinolone. This regimen aims to effectively target the two most common pathogens in sCAP, Streptococcus pneumoniae and Legionella (19,29). Although both macrolides and respiratory fluoroquinolones are active against atypical bacteria, macrolides are generally preferred. A systematic review and meta-analysis involving 9,850 critically ill CAP patients showed an 18% relative reduction in mortality when macrolides were included in the treatment compared to regimens without them *(34)*. Additionally, studies on hospitalized CAP patients demonstrated that combining a beta-lactam with a macrolide lowered the need for mechanical ventilation and decreased mortality *(35,36)*. These benefits are attributed to the immunomodulatory properties of macrolides, which influence pro-inflammatory cytokines such as tumor necrosis factor, interleukins 1, 6, 8, and interferon-γ, as well as reduce T-cell-mediated immunity and neutrophil functions like chemotaxis, adhesion, and oxidative activity. Furthermore, macrolides inhibit biofilm formation and decrease mucus production, enhancing mucociliary clearance *(37)*.

All patients admitted to the ICU should undergo urinary antigen testing for *Legionella*. Patients with Legionnaires' disease are treated only with azithromycin or a respiratory fluoroquinolone. In patients with risk factors for *Pseudomonas aeruginosa* infection, treatment is carried out with antipseudomonas antibiotics. It is necessary to apply a combination of antibiotics from two different groups, namely a beta-lactam antibiotic (piperacillin-tazobactam, ceftazidime, cefepime) in combination with ciprofloxacin or a carbapenem (imipenem, meropenem) *(14)*.

In our country, in principle, *MRSA* is an uncommon causative agent of CAP. If is detected, it is treated with vancomycin or linezolid *(14)*.

Treatment with oseltamivir is recommended for patients with PCR-proven influenza infection. Also, if testing is not available, oseltamivir should be used in patients with sCAP during the flu season *(29)*. A meta-analysis involving over 5,000 ICU patients with influenza A H1N1 pneumonia found that treatment with neuraminidase inhibitors was linked to a reduction in mortality. The greatest benefit was observed when treatment was started early—within two days of symptom onset—compared to later initiation or no treatment at all *(38)*.

ADDITION OF GLUCOCORTICOIDS IN THE TREATMENT OF CAP

Despite improvements in antibiotic therapy, mortality rates among hospitalized patients with CAP remain high. In cases of sCAP complicated by lung injury and acute respiratory distress syndrome (ARDS), mortality exceeds 30% *(23)*. An exaggerated inflammatory response from the host is linked to poor treatment outcomes and increased risk of death *(39,40)*. Corticosteroids are used in sCAP because they suppress the production of multiple proinflammatory cytokines, thereby reducing inflammation-induced lung damage.

Current guidelines recommend corticosteroid use for patients with sCAP accompanied by shock. When considered, methylprednisolone at a dose of 0.5 mg/kg every 12 hours for 5 days is an appropriate choice *(29)*.

Several studies have explored corticosteroid therapy in sCAP. A randomized controlled trial in patients with sCAP and elevated inflammatory markers (CRP >150 mg/L) compared methylprednisolone to placebo over 5 days. The results showed that methylprednisolone reduced treatment failure rates, mechanical ventilation requirements, and incidence of septic shock *(41)*. Additional smaller trials examining hydrocortisone as an adjunct therapy demonstrated significant reductions in ICU mor-

tality, shock, length of mechanical ventilation, and the number of patients needing ventilation (29). While corticosteroid side effects were not extensively monitored, some increase in blood glucose levels was noted, without a rise in gastrointestinal bleeding incidents *(42)*.

However, corticosteroids are not recommended for patients with sCAP caused solely by influenza or influenza combined with bacterial co-infection (29). A meta-analysis including 19 studies and over 3,000 patients with influenza pneumonia found that corticosteroid treatment was associated with a threefold increase in mortality risk *(42)*.

CONCLUSION

Severe CAP is a major global health concern that requires prompt recognition and aggressive management. Advances in diagnostic tools, antimicrobial therapy, and critical care interventions have improved survival rates, sCAP continues to pose significant challenges. Prioritizing prevention, timely diagnosis, and personalized treatment approaches is crucial for lowering mortality rates and enhancing patient outcomes. Ongoing research and public health initiatives remain vital in addressing the evolving epidemiology of sCAP and mitigating its impact on global healthcare systems.

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