DOI: 10.66069/ojspub.27450830

From Diagnosis to Treatment: Advances in Clinical Research on Severe Pneumonia

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Abstract: ***Severe pneumonia is a life-threatening infectious disease associated with high mortality and is frequently complicated by acute respiratory distress syndrome, septic shock, and multiple organ dysfunction. The current diagnostic and therapeutic paradigm is shifting from empirical broad-spectrum treatment toward individualized management based on precise pathogen identification and assessment of the host response. The pathogenesis of severe pneumonia involves a broad range of bacterial, viral, and fungal pathogens, together with complex pathophysiological processes including dysregulated inflammation, immune dysfunction, and coagulation abnormalities. Conventional pathogen-detection methods are limited by low sensitivity and prolonged turnaround times. Emerging molecular diagnostic technologies have substantially increased pathogen detection rates and facilitated early, targeted anti-infective therapy, while biomarkers have improved inflammatory monitoring and prognostic assessment. This review summarizes contemporary evidence on the etiological features of severe pneumonia, advances in diagnostic technologies, optimization of treatment strategies, and integrated models of care, with the aim of providing a theoretical basis for improved clinical management and outcomes.***

Keywords: Severe pneumonia, Etiology, Metagenomic next-generation sequencing, Precision therapy, Multidisciplinary collaboration**.**

1. Introduction

Severe pneumonia (SP) remains a major focus of clinical medicine. Published studies have reported a 30-day mortality rate of 23%–47% [1–3], making it one of the leading causes of death among patients admitted to intensive care units (ICUs). According to the World Health Organization's 2024 report, COVID-19 and lower respiratory tract infections ranked second and fifth, respectively, among the ten leading causes of death worldwide in 2021. Severe pneumonia has heterogeneous clinical manifestations, and its pathogen distribution varies among patient populations. Rapid pathogen identification and timely initiation of targeted anti-infective therapy are therefore essential for reducing mortality, improving prognosis, and limiting healthcare expenditure [4].

Severe pneumonia usually presents with systemic manifestations as well as signs and symptoms involving the lungs and related structures. Patients may develop high fever, rigors, night sweats, or a productive cough; sputum may be mucoid, purulent, or blood-streaked. Dyspnea and pleuritic chest pain may occur. Other systemic symptoms include fatigue, headache, myalgia, and arthralgia. Confusion or altered mental status is especially common in older adults. Physical examination may reveal tachycardia, tachypnea, and hypotension, with frequently severe hypoxemia. Body temperature may be extremely high or abnormally low. Septic shock and signs of end-organ failure are common, and auscultation may disclose crackles and bronchial breath sounds [5].

Severe pneumonia poses a formidable global public-health challenge because of its high incidence and mortality and its complex clinical and pathophysiological course. Lower respiratory tract infections have consistently ranked among the ten leading causes of death worldwide, and severe pneumonia—the most critical manifestation of these infections—is a major cause of septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS). It therefore imposes sustained pressure on healthcare resources and the broader economy.

For many years, clinical management relied heavily on empirical diagnosis and broad-spectrum antimicrobial coverage. Although this approach has historically saved lives, its inherent lack of specificity has produced serious consequences. Antimicrobial overuse increases selective pressure and has directly contributed to the global spread of multidrug-resistant organisms, including carbapenem-resistant Enterobacterales, Acinetobacter baumannii, and methicillin-resistant Staphylococcus aureus. Conversely, inadequate or delayed coverage of viruses, atypical pathogens such as Mycoplasma pneumoniae and Legionella species, and fungi may lead to failure of initial treatment.

The etiological landscape is undergoing profound change. Conventional bacterial pathogens remain prevalent, while the emergence of novel viruses such as SARS-CoV-2 and the re-emergence of atypical pathogens have made the pathogen spectrum increasingly complex and have challenged the accuracy of empirical therapy. This difficulty is driving a fundamental transition from nonspecific empirical coverage toward evidence-based, precise, individualized, and integrated management.

This transition is not an isolated technological upgrade; rather, it reflects convergent advances in molecular biology, genomics, immunology, and information technology. Culture-independent diagnostic methods such as metagenomic next-generation sequencing (mNGS) can provide unbiased detection of microbial nucleic acids in a sample within 24–48 hours, substantially improving etiological diagnosis in diagnostically challenging, critically ill, and immunocompromised patients. A prospective multicenter randomized controlled trial published in 2024 provided landmark evidence for mNGS, reporting an increase

in the pathogen-detection rate for severe community-acquired pneumonia in the ICU from 38.8% with conventional methods to 79.9%; mNGS also supported more appropriate antimicrobial adjustment and shortened the time to clinical improvement.

Meanwhile, multiplex polymerase chain reaction (PCR), serial monitoring of inflammatory and immune biomarkers such as interleukin-6 (IL-6) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), pharmacokinetic/ pharmacodynamic (PK/PD)-guided dosing, artificial intelligence (AI)-assisted imaging, and prognostic models are collectively creating a modern diagnostic and therapeutic loop—from rapid pathogen identification, through assessment of the host response, to targeted intervention. A systematic review of recent advances in pathogen epidemiology, diagnostics, treatment, and care pathways is therefore essential for guiding clinical practice, optimizing resource allocation, and ultimately improving outcomes. Following the central theme of progression from etiology to integrated management, this review examines key evidence and future directions to provide clinicians with an up-to-date evidence-based reference.

2. Contemporary Etiological Features and Challenges

The etiological profile of severe pneumonia is changing in profound and complex ways. Its defining features may be summarized as the spread of antimicrobial resistance and the re-emergence of pathogens, which together constitute a central challenge for contemporary diagnosis and treatment.

2.1 The Growing Burden of Antimicrobial-resistant Infections

Bacterial resistance has become a major determinant of outcomes and healthcare-resource utilization among ICU patients. The current trend toward extensive and even extreme drug resistance is particularly concerning among Gram-negative bacilli. Inadequate infection-control measures and antibiotic selective pressure are two major drivers of resistance. Substantial evidence demonstrates that antibiotic exposure directly promotes the development of resistance, reinforcing the need to eliminate inappropriate prescribing [6].

Infections caused by resistant organisms, particularly hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), represent a major threat in the ICU. Surveillance data from China and other countries indicate that Gram-negative bacilli predominate. Detection rates of carbapenem-resistant A. baumannii (CRAB) and carbapenem-resistant Klebsiella pneumoniae (CRKP) remain high. In some regions of China, resistance of CRAB to carbapenems exceeds 70%, while the corresponding rate for CRKP remains at approximately 25%. Methicillin-resistant S. aureus (MRSA) also remains epidemiologically important. These ‘superbugs’ markedly increase the likelihood of failure of initial empirical therapy and are directly associated with prolonged hospitalization, higher costs, and increased mortality.

2.2 Challenges Posed by Atypical and Re-emerging Pathogens

Streptococcus pneumoniae, Haemophilus influenzae, and S. aureus are recognized as common causes of community-acquired pneumonia (CAP) and are traditionally considered ‘typical’ pathogens [3]. Evidence-based epidemiological investigation of pneumonia is complex, and the causative microorganism remains unidentified in nearly 60% of cases [3,6]. With widespread use of pneumococcal conjugate vaccines and the emergence of multidrug-resistant organisms, the microbial causes of pneumonia have changed over recent years. Moraxella catarrhalis, M. pneumoniae, Chlamydia pneumoniae, and Legionella species are now also recognized as common causes of CAP. Improved recognition of other pathogens, especially viruses that frequently coexist with bacterial respiratory infections [12], has introduced additional variables and challenges into pneumonia management.

From a clinical perspective, atypical pneumonia may be classified by route of transmission as nonzoonotic or zoonotic. Infections caused by M. pneumoniae, C. pneumoniae, and Legionella pneumophila are the most common causes of nonzoonotic atypical bacterial pneumonia. Because these pathogens are difficult to isolate and culture, the frequency of coinfection in patients with CAP is high but difficult to estimate accurately. Zoonotic pneumonia is uncommon in the general population and is closely associated with specific environmental exposures or animal vectors. Chlamydia psittaci, Francisella tularensis, and Coxiella burnetii are among the most common zoonotic causes and are important CAP pathogens in selected immunocompetent populations [7].

Viral pneumonia comprises a broad group of infections caused by viruses that commonly affect the upper and lower respiratory tracts. The true contribution of viruses as a sole cause of CAP is probably underestimated because of limited testing and because nasopharyngeal or oropharyngeal swab PCR may yield negative results. Nevertheless, a large meta-analysis reported that viral infection accounted for as many as 44% of pneumonia cases in the general population [8].

Given their distinctive clinical, epidemiological, and therapeutic features, viral infections may reasonably be included within the spectrum of atypical pneumonia. Influenza viruses, parainfluenza viruses, respiratory syncytial virus (RSV), adenoviruses, and human metapneumovirus (HMPV) are the most common viral causes of CAP.

Viruses are also frequent causes of severe pneumonia, community outbreaks, and global respiratory pandemics. Viruses responsible for major community outbreaks include avian influenza viruses (H5, H7, and H9 subtypes), severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and, most recently, SARS-CoV-2. Although animal-to-human transmission has been identified as the initial source for each of these viruses, the resulting infections are not generally classified as zoonoses once sustained human transmission occurs. During major outbreaks, person-to-person spread via respiratory droplets occurs to varying degrees, with avian influenza viruses showing the least efficient human-to-human transmission. Hantaviruses are not transmitted between humans and are therefore considered true zoonotic infections.

3. A Paradigm Shift in Diagnostic Technologies

Accurate diagnosis is the foundation of individualized therapy. In recent years, diagnostic practice has moved beyond reliance on slow conventional cultures into an era dominated by molecular biology and omics technologies that seek to provide rapid, accurate, and comprehensive results.

3.1 Molecular Diagnostics as a Mainstay of Clinical Practice

PCR is increasingly regarded as a highly sensitive new reference standard. Most assays can detect fewer than 100 colony-forming units per milliliter and offer high specificity without cross-reactivity [9].

Severe CAP (SCAP) and HAP/VAP are frequently accompanied by serious complications and high mortality, creating a substantial burden on healthcare systems. Because many common SCAP pathogens are difficult to culture, sensitive and rapid nucleic-acid detection methods — including PCR and next-generation sequencing (NGS)—play an important role in etiological diagnosis. PCR may be performed as a singleplex or multiplex assay, enabling rapid pathogen detection at relatively low cost. Single-target nucleic-acid tests have been particularly important during epidemics of influenza, COVID-19, and M. pneumoniae infection [10]. Commercial multiplex PCR panels targeting common respiratory pathogens can rapidly test for a predefined group of organisms.

Before nucleic-acid amplification tests became available, viral respiratory infections were diagnosed mainly by serological methods, including demonstration of a substantial rise in antibody titers by complement fixation, detection of viral antigens by immunofluorescence or colorimetric assays, and viral isolation in cell culture—often followed by blind passage and immunofluorescence or hemadsorption testing [11,12]. These traditional methods retain value when rapid results are not essential [13].

Over the past two decades, advances in genomic amplification have markedly increased the sensitivity and specificity of respiratory-virus detection. Several novel respiratory viruses have been identified, and sensitive PCR assays have been developed for them [14]. These advances enabled multiplex PCR, in which multiple primer sets are used within a single reaction, substantially reducing the time required compared with serial single-target assays. Both singleplex and multiplex PCR rapidly detect respiratory viruses in clinical specimens and have been used to define the epidemiology of emerging viruses, including the 2009 influenza A(H1N1) virus and MERS-CoV in 2012. Multiple commercial multiplex panels can identify several viruses in a single test and continue to undergo optimization and evaluation.

Basic laboratory diagnosis of respiratory viral infection is increasingly being integrated with viral subtyping, antiviral-resistance testing, nucleotide-polymorphism analysis, and viral-load measurement, thereby providing more comprehensive information to support optimal treatment [10].

3.2 mNGS is Reshaping the Diagnosis of Complex Infections

Metagenomic next-generation sequencing is an emerging method for microbial identification. It characterizes the DNA or RNA present in a specimen, permitting analysis of the entire microbial community and rapid identification of clinically relevant pathogens [15,16]. Compared with conventional methods, mNGS offers broad pathogen coverage, short turnaround times, and high analytical sensitivity.

Chen et al. reported that mNGS of bronchoalveolar lavage fluid (BALF) detected a broader pathogen spectrum than culture, including more fungi and viruses. The turnaround time for mNGS was approximately 2 days, compared with 3 days for bacterial culture, 7 days for fungal culture, and 45 days for mycobacterial culture [17]. However, mNGS also has important limitations, and a molecular result alone cannot serve as a definitive clinical diagnosis. The respiratory tract is colonized by numerous microorganisms; therefore, organisms detected by mNGS must be classified as probable pathogens, colonizers, or contaminants [18]. Interpretation requires integration of clinical presentation, immune status, and underlying disease.

Xing et al. [4] found high mNGS read counts for Stenotrophomonas maltophilia, Corynebacterium striatum, Enterococcus species, and Candida species; however, these organisms are often opportunistic and rarely cause severe lower respiratory tract infection. Human herpesviruses and anelloviruses were also detected in many cases but generally did not cause pneumonia and provided limited guidance for treatment. Pathogen identification alone is therefore insufficient. Detection of clinically relevant antimicrobial-resistance genes (ARGs) is needed to predict resistance and guide management. Although culture-independent mNGS is attractive, most platforms rely on short-read sequencing, making it difficult to determine whether a detected ARG originates from the genome of a causative pathogen, the normal microbiota, or environmental contamination [18]. Substantial technical and interpretive barriers remain.

NGS approaches primarily include mNGS and targeted next-generation sequencing (tNGS). Unlike PCR, mNGS does not require prespecification of candidate pathogens and can detect emerging, rare, or previously unknown organisms; in principle, it can cover nearly the entire range of microbial pathogens. It is therefore particularly valuable for etiological diagnosis in SCAP and in immunocompromised patients with CAP [19].

3.3 Biomarkers: from Diagnosis to Prognostication and Treatment Guidance

Procalcitonin (PCT) and C-reactive protein (CRP) are commonly used biomarkers in severe pneumonia. As acute-phase reactants, both increase during inflammation, particularly in response to bacterial pathogens. PCT may rise on the first day after symptom onset, whereas CRP often increases by the third day. Regardless of their initial values, neither marker should be used in isolation to determine whether antibiotics should be initiated. When combined with clinical judgment, serial PCT measurement can guide shorter

antibiotic courses and has been associated with lower mortality [5].

PCT-guided management can reduce treatment duration and defined daily antibiotic doses among critically ill patients with presumed bacterial infection. This reduction has been associated with a significant decrease in mortality. PCT concentrations may help clinicians determine whether a suspected infection is genuinely bacterial, prompting more appropriate diagnostic evaluation and treatment—an essential element of antimicrobial stewardship [20].

PCT has also been used to guide decisions about initiating antibiotics in patients with lower respiratory tract infections, although most studies were not restricted to patients with radiographically confirmed pneumonia. Some patients with CAP and low PCT levels have been managed safely without antibiotics, but the available evidence derives from small subgroups and raises safety concerns regarding widespread adoption of this strategy [21].

Biomarker research has expanded beyond CRP and PCT. Serial IL-6 measurement may help quantify the systemic inflammatory response and identify patients at high risk of a cytokine storm. Newer markers, including sTREM-1 and heparin-binding protein (HBP), show promise for distinguishing infection from noninfectious lung injury and predicting disease severity. In the future, biomarker signatures derived from multi-omics platforms such as proteomics and metabolomics, combined with machine-learning algorithms, may enable early risk stratification and more precise prognostic prediction.

4. Treatment Strategies: Toward Precision and Integration

In response to the complex interplay between pathogens and the host response, treatment has evolved beyond antimicrobial therapy alone into an integrated system encompassing targeted anti-infective therapy, immune modulation, and advanced organ support.

4.1 Precision Approaches to Anti-infective Therapy

When risk factors for MRSA or Pseudomonas aeruginosa are present, sputum should be obtained for Gram staining and culture regardless of whether the initial empirical regimen includes expanded coverage for these pathogens. If expanded coverage is started, negative microbiological results can support de-escalation; if coverage is not initially provided, positive results can guide modification of therapy. Although many individual risk factors for MRSA and P. aeruginosa have been reported, many associations are weak and vary geographically. The most consistently strong risk factor is previous infection with either organism. Hospitalization with parenteral antibiotic treatment during the preceding 90 days is also associated with increased risk, and sputum culture is therefore recommended in this setting.

These recommendations are not based on high-quality evidence, but they reflect efforts to improve antibiotic use and increase clinicians' awareness of local pathogen prevalence and resistance patterns—information that is crucial to selecting appropriate empirical therapy. Further research is needed. Rapid, cost-effective, sensitive, and specific tests that identify the causative organism in CAP may improve routine care by facilitating targeted therapy, particularly in patients with risk factors for resistant pathogens. All new diagnostic technologies require evaluation in high-quality studies to determine their effects on treatment decisions and patient outcomes [21].

Targeted therapy based on rapid etiological results, especially molecular and mNGS findings, is a core principle. Strategies for resistant infections must be individualized. For pneumonia caused by carbapenem-resistant Gram-negative organisms, for example, intravenous polymyxin B or colistin may be combined with inhaled administration to increase local drug concentrations in lung tissue. Therapeutic drug monitoring (TDM), antimicrobial-susceptibility results, and population PK/PD models can then be used to individualize dosing while balancing efficacy against nephrotoxicity and neurotoxicity.

4.2 Modulation of the Host Immune Response

An excessive host immune response to infection is a central component of the pathophysiology of severe pneumonia. Appropriately selected glucocorticoids, such as dexamethasone or methylprednisolone, can suppress excessive inflammation and may improve outcomes in critically ill patients; supporting evidence is strongest for selected viral pneumonias, including COVID-19, and for certain bacterial pneumonias. In the future, biologic agents targeting specific cytokines such as IL-1 or IL-6 may play a larger role in precision immunomodulation.

4.3 Integration of Organ-support Strategies

Robust organ support provides the physiological foundation for anti-infective therapy and immune modulation. Supportive care includes individualized respiratory support—ranging from high-flow nasal oxygen and noninvasive ventilation to invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO)—as well as carefully titrated fluid management, hemodynamic support, nutritional therapy, and early rehabilitation. Together, these measures form the life-sustaining platform of severe-pneumonia management.

5. Integrated Care Pathways and Future Directions

Future management of severe pneumonia will necessarily integrate advanced technologies with multidisciplinary teamwork. The ideal pathway is a patient-centered closed loop: rapid and accurate diagnosis with multiplex PCR or mNGS provides the starting point; serial biomarkers such as PCT and cytokines, together with clinical scores, guide ongoing assessment; and a multidisciplinary team—including specialists in respiratory and critical care medicine, infectious diseases, clinical microbiology, pharmacy, and imaging —collaborates in real time to deliver individualized anti-infective therapy, immune modulation, and organ support. Management is then repeatedly adjusted according to the patient's response.

Further optimization of nanopore sequencing may enable

faster bedside pathogen detection. Applications of AI in image interpretation, multidimensional data integration, and prognostic modeling are likely to expand. New antimicrobial agents—including novel β-lactam/β-lactamase inhibitor combinations active against multidrug-resistant organisms — together with bacteriophage therapy and more precise immunomodulatory agents, will broaden the therapeutic armamentarium.

6. Conclusions

The diagnosis and treatment of severe pneumonia have entered an era of precision and integrated management. Increasing etiological complexity is the principal force driving this transition, while advances in molecular diagnostics, biomarkers, and precision pharmacotherapy have made it possible to move beyond empirical broad-spectrum treatment toward management tailored to both pathogen and host characteristics. Improving outcomes requires a modern clinical system capable of rapidly integrating etiological information, host-response profiles, and multiorgan functional data and translating them into dynamic, individualized interventions. Clinicians must continually update their knowledge, adopt validated technologies, and work within multidisciplinary teams to develop the optimal strategy for each patient with severe pneumonia.

7. Outlook

During treatment monitoring and adjustment, serial changes in biomarkers such as IL-6 and PCT can be used to assess response, while antimicrobial-susceptibility results inform modification of antibiotic regimens. For prognostic assessment, scoring systems such as the Sequential Organ Failure Assessment (SOFA), integrated with multi-omics analyses, can characterize organ function and prognosis and guide subsequent decisions.

As precision medicine advances, diagnostic testing for severe pneumonia will increasingly emphasize the integration of multi-omics data, AI-assisted analysis, and rapid point-of-care testing, thereby accelerating the transition toward more precise and individualized diagnosis and treatment.

Fund Project

National Natural Science Foundation of China (No. 81960508).

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