Literature Review

Optimizing Early Recognition and Management of Sepsis Secondary to Pneumonia: A Literature Review

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Abstract

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, frequently complicates pneumonia, a leading global cause of morbidity and mortality. This review synthesizes current evidence on optimizing early recognition and management of sepsis secondary to pneumonia, highlighting critical diagnostic and therapeutic strategies. *Streptococcus pneumoniae* remains the predominant pathogen in community-acquired pneumonia (CAP), though antimicrobial resistance and atypical organisms pose growing challenges. Key risk factors include comorbidities (e.g., renal/liver disease, diabetes), immunosuppression, and socioeconomic determinants. Early diagnosis combines clinical assessment (e.g., SOFA, qSOFA scores) with biomarkers like procalcitonin, lactate, and neutrophil-to-lymphocyte ratio (NLR). Innovative tools, such as artificial intelligence (AI)-driven analysis of blood count data, show promise for rapid sepsis detection. The cornerstone of management is the "1-hour bundle": immediate broad-spectrum antibiotics (tailored to local resistance patterns), fluid resuscitation with crystalloids, and vasopressors for refractory hypotension. Antibiotic selection must account for pathogen profiles, with macrolides or fluoroquinolones recommended for severe CAP. Fluid balance is critical to avoid pulmonary edema, while organ support (e.g., mechanical ventilation) is often required for respiratory failure. Despite therapeutic advances, sepsis mortality remains high (24–65% in Indonesia), driven by delays in treatment and comorbid conditions. Survivors frequently face long-term physical and cognitive impairments, necessitating comprehensive rehabilitation. Future efforts should prioritize rapid diagnostics, personalized therapy, and post-sepsis care to improve outcomes. This review underscores the importance of early, protocol-driven interventions to mitigate the global burden of sepsis complicating pneumonia.

Keywords: antibiotics, management, pneumonia, sepsis

INTRODUCTION

Sepsis is a life-threatening condition marked by organ dysfunction resulting from a dysregulated host response to infection. When it progresses to septic shock, the risk of mortality increases substantially, especially in the absence of timely and effective treatment. Since the first international consensus definition in 1991, the global incidence of sepsis and septic shock has steadily increased. An estimated 49 million cases and 11 million sepsis-related deaths were reported worldwide in 2017.[1,2] Sepsis can arise from infections in various organ systems, with lower respiratory tract infections—particularly pneumonia—being the most common cause.[3]

Pneumonia remains a leading cause of global morbidity and mortality, particularly among children under five years of age, with approximately 120 million cases worldwide. Diagnosis relies heavily on clinical presentation and radiographic findings, yet the causative pathogen is frequently unidentified. This poses a major challenge, especially in managing community-acquired pneumonia (CAP), as no single antimicrobial regimen covers the full spectrum of potential pathogens. Further complicating treatment is the geographical variability in antimicrobial resistance, necessitating region-specific empirical therapy.[4]

But, sepsis and septic shock remain pressing worldwide health concerns, exerting substantial pressure on medical facilities, particularly emergency rooms and intensive care units (ICUs). The rising prevalence of these conditions stems from multiple drivers, such as demographic shifts toward older populations, increasing rates of chronic illnesses, widespread use of invasive treatments, and escalating antibiotic resistance.

Adding to the epidemiological burden, sepsis treatment presents unique challenges due to the complex interactions between various biological systems, including pathological, cellular, genetic, and immune mechanisms that influence disease development. While modern intensive care techniques and standardized treatment approaches have enhanced results for patients, timely identification and immediate intervention continue to be vital determinants of survival rates.

DEFINITION

Sepsis is a life-threatening clinical syndrome characterized by organ dysfunction due to a dysregulated host response to infection. Its most severe subset, septic shock, involves profound circulatory, cellular, and metabolic derangements, requiring vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg.[1]

It is known that CAP, as a primary contributor to sepsis development, is characterized by acute lung tissue infection developing outside medical facilities and represents the predominant form of pneumonia.[4] Research indicates respiratory infections trigger 40-50% of all sepsis cases, with CAP serving as the most

frequent underlying source.[5] This significant disease burden underscores the critical need for thorough clinical evaluation in CAP patients, enabling prompt identification of those at elevated risk and implementation of appropriate interventions to improve prognosis.

EPIDEMIOLOGY

According to the Global Burden of Disease Study 2021, lower respiratory infections caused about 2.2 million deaths, making them the seventh biggest cause of death around the world. Among the bacteria that cause these infections, *Streptococcus pneumoniae* is the main one, leading to around 505,000 deaths each year.[5]

Then come *Staphylococcus aureus*, which causes about 424,000 deaths annually, and *Klebsiella pneumoniae*, responsible for around 176,000 deaths per year. On the viral side, respiratory syncytial virus (RSV) continues to be a big cause, leading to 33 million cases of lower respiratory infections and 3.6 million hospital visits for children under five every year.[5]

Similar age-dependent patterns are observed in Europe, where the annual CAP incidence ranges from 1.07-1.2 cases per 1,000 population overall, but rises to approximately 14 per 1,000 among adults ≥65 years. Notably, males consistently show higher pneumonia incidence across all age groups in both regions.[6,7] Asian epidemiological data reveal comparable trends, with multicenter studies reporting an overall CAP incidence of 16.9 per 1,000 adults annually with persistent male predominance (15.6 vs. 9.3 per 1,000).[6,8]

According to Sitaruno et al, in a study conducted in a Thai medical ICU, 19.2% of all ICU admissions were due to sepsis or septic shock, with pneumonia (specifically respiratory tract infections). Among the 123 patients studied, 70.7% had sepsis, while 29.3% progressed to septic shock, with hospital mortality rates reaching 47.2% in the shock group.[7] However, significant regional variations exist, with central Vietnam documenting 0.81 per 1,000, and Singapore showing pneumococcal pneumonia incidence of 4.5 per 100,000 among adults aged 15-64 years.[3]

The study by Yiang et al further explored the epidemiology of multidrug-resistant organisms (MDROs) in pneumonia patients with septic shock. Among 533 patients admitted to the emergency department, those with risk factors for MDROs had a significantly higher incidence of infections caused by *Pseudomonas aeruginosa* and carbapenem-resistant pathogens, leading to worse outcomes and higher ICU mortality if not managed promptly.[9] Despite these findings, a notable research gap persists regarding direct comparisons of CAP and hospital-acquired pneumonia (HAP) incidence across Southeast Asian nations.[3]

ETIOLOGY

Sepsis arises from diverse microorganisms, with bacterial pathogens

predominating. Epidemiologic patterns demonstrate significant geographic variation. Gram-negative bacteria cause 60-70% of sepsis cases in developing nations, whereas Gram-positive organisms are increasingly prevalent in developed countries like the United States because of rising rates of invasive procedures, HAP, and antimicrobial resistance. Although fungal sepsis incidence is growing, it remains less common than bacterial etiologies.[10]

Streptococcus pneumoniae remains the leading cause of CAP in adults worldwide, accounting for more than 90% of confirmed cases. Atypical pathogens such as *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydia psittaci* are responsible for approximately 22% of cases, underscoring the importance of broad diagnostic strategies.[11]

In immunocompromised patients, the microbial landscape shifts significantly, with a notably higher prevalence of antibiotic-resistant organisms, including *Enterobacteriaceae*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and extended-spectrum β-lactamase (ESBL)-producing bacteria, compared to those with intact immune systems. These findings highlight the need to evaluate both the patient's immune status and regional resistance patterns when selecting empirical antibiotics for pneumonia treatment.[11]

RISK FACTORS

A nationwide study conducted in Sweden identified several comorbidities as significant risk contributors to sepsis requiring intensive care. End-stage renal disease emerged as the strongest risk factor, with an odds ratio (OR) of 6.09 (95% CI=3.52–10.54), followed by moderate to severe liver disease (OR=7.84; 95% CI=5.70–10.79).[12]

Malignancy also demonstrated a strong association with sepsis risk (OR=4.30; 95% CI=3.71–4.99), as did substance abuse (OR=3.50), congestive heart failure (OR=2.67), and diabetes with complications (OR=2.65) and without (OR=1.98). Additional notable risk factors included chronic obstructive pulmonary disease (COPD) with an OR of 2.09.[12]

The analysis of over 169,000 participants across 29 high-quality studies revealed that certain exposures dramatically increase odds. Immunosuppressive therapy presents the most formidable threat by more than tripling the risk (OR=3.1). Other major modifiable factors include poor oral health, which nearly triples the odds (OR=2.78), and smoking, which increases them by over 50% (OR=1.57). Furthermore, common medical treatments like oral steroids (OR=1.87) and gastric acid-suppressive drugs (OR=1.51) were also identified as significant contributors.[13]

The combination of serum lactate levels and the PaO_2/FiO_2 (PF) ratio was particularly effective in predicting mortality. Patients with a PF ratio <170 and lactate ≥3.5 mmol/L had the worst prognosis. Other significant predictors of mortality included cardiopulmonary resuscitation (OR=4.20), serum lactate levels ≥3.5

mmol/L (OR=1.92), and a high sequential organ failure assessment (SOFA) score ≥12 (OR=2.41).[14]

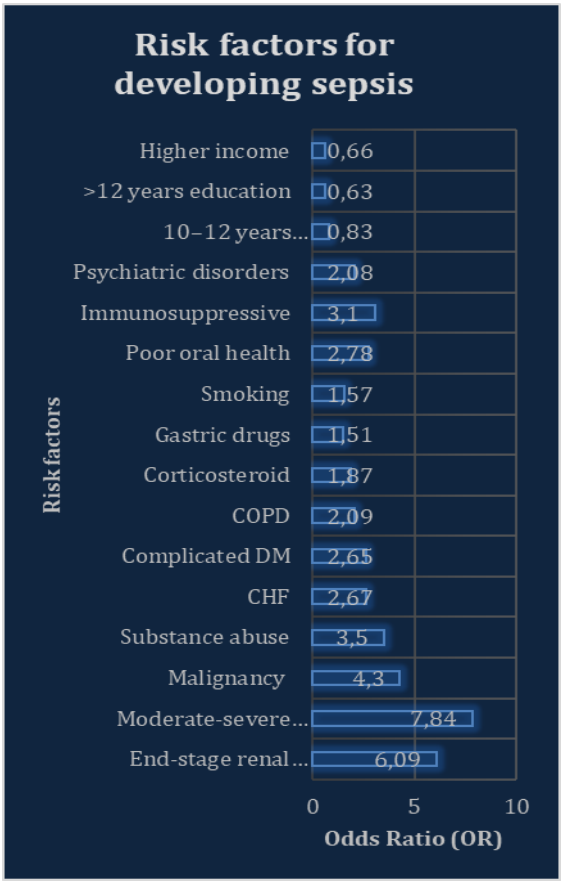


Figure 1. Risk factors for developing sepsis vary from non-medical factors and medical comorbidities.[12,13]

In a separate study by Gai et al, similar results were obtained with the focus on identifying prognostic indicators associated with mortality in ICU patients with sepsis. Non-survivors had significantly higher APACHE II scores (22.67 vs. 17.43), SOFA scores (10.62 vs. 7.83), and serum lactate levels (3.79 vs. 2.74 mmol/L) compared to survivors (P<0.001), emphasizing the value of these parameters in predicting sepsis outcomes.[15] In study by Kim et al also supports these findings, sepsis patients with pneumonia had a higher need for mechanical ventilation, lower PF ratios, and higher simplified acute physiology score (SAPS II) scores, indicating greater illness severity.[16]

Beyond traditional medical comorbidities, psychiatric conditions and socioeconomic factors independently contribute to sepsis vulnerability. Psychiatric disorders demonstrate a significant association with sepsis development (OR=2.08), comparable in magnitude to many biological risk factors.[12]

Socioeconomic determinants reveal a striking protective gradient, where individuals completing 10-12 years of education show reduced risk (OR=0.83), while those with >12 years of education exhibit even greater protection (OR=0.63). Similarly, higher income brackets correlate with substantially lower sepsis incidence versus lower income groups (OR=0.66).[12]

Notably, in patients without somatic comorbidities, substance use disorders (OR=3.50) and psychiatric illness (OR=1.89) maintain strong independent associations with sepsis risk, confirming their direct pathophysiological role beyond mere comorbidity clustering. These findings establish that psychosocial determinants, including mental health status, educational attainment, and economic resources, represent modifiable risk factors requiring integration into comprehensive sepsis prevention strategies.[12,15]

PATHOGENESIS

The pathogenesis of sepsis involves a complex interplay between pathogens,

host immune responses, and inflammatory mediators. In response to an invading pathogen, the immune system initiates a defense mechanism aimed at eradicating the infectious agent. Despite considerable differences in structure, virulence, and mechanisms of infection among viruses, parasites, fungi, and bacteria, all these pathogens share conserved molecular motifs known as pathogen-associated molecular patterns (PAMPs).[16]

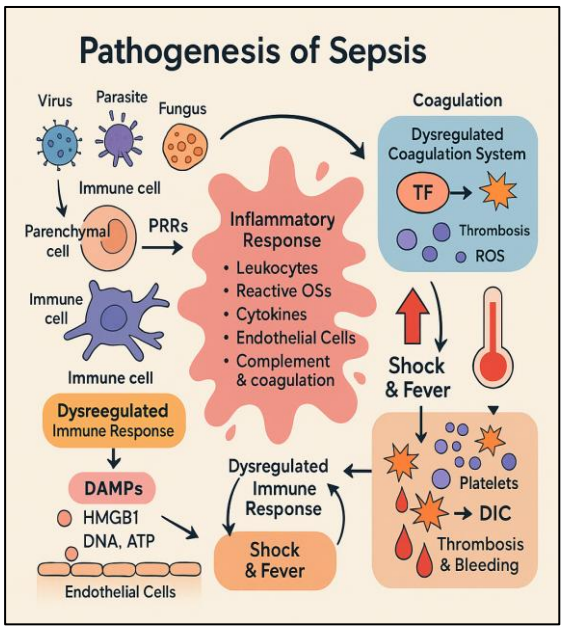
Sepsis begins when pathogens breach host barriers (e.g., lungs in pneumonia) and release PAMP, such as lipopolysaccharides (LPS) and bacterial DNA.[17,18] These PAMPs act as recognizable signals and are detected by pattern recognition receptors (PRRs), which are expressed by a variety of immune and parenchymal cells. Key families of PRRs include Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NOD-like receptors or NLRs), among others.[19,20]

Sepsis develops when the initial immune response to infection becomes dysregulated, progressing from a protective mechanism to a harmful systemic reaction. Upon detecting PAMPs through PRRs, immune cells activate inflammatory pathways that normally clear infections. However, when pathogens evade elimination, persistent PRR stimulation leads to excessive production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and impaired anti-inflammatory regulation.[16,21] This imbalance causes widespread endothelial damage and microvascular dysfunction. Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) driven endothelial inflammation causes leukocyte extravasation, thrombus formation, and capillary leakage.[21]

The pathological process is further amplified by damage-associated molecular patterns (DAMPs) - including High Mobility Group Box 1 (HMGB1), heat shock proteins, nucleic acids, and metabolites (ATP, uric acid) released from injured host cells.[22] These DAMPs perpetuate inflammation through additional PRR activation, creating a vicious cycle of cellular injury, coagulopathy, and ultimately, multi-organ failure characteristic of severe sepsis. The simultaneous presence of both PAMPs and DAMPs explains the transition from localized infection to life-threatening systemic illness, highlighting the complex interplay between microbial invasion and host response in sepsis pathogenesis.[19,20]

The systemic hyperinflammatory response in sepsis clinically presents with fever and circulatory shock, representing the culmination of complex interactions between multiple pathophysiological components. This maladaptive response involves coordinated activation of leukocytes (particularly neutrophils and macrophages), cytokine networks, reactive oxygen species (ROS), endothelial cells, and the interconnected complement and coagulation cascades. While localized activation of these pro-inflammatory and pro-coagulant pathways serves a protective role in contained infections, their systemic dysregulation becomes pathogenic in sepsis.[22]

Key mediators include TNF-α and interleukin-1β (IL-1β), whose uncontrolled activity drives widespread tissue injury through multiple mechanisms. Activated neutrophils further amplify this damage through the release of ROS and proteolytic enzymes (e.g., elastase, matrix metalloproteinases), creating a self-perpetuating cycle of inflammation and cellular injury that characterizes severe sepsis.[15,19]



Note: TF: Transfer Factor; PRRs: Pattern Recognition Receptors; OSs: Oxidative Stress; DAMPs: Damage-Associated Molecular Patterns; HMGB1: High-Mobility Group Box 1; DNA: Deoxyribonucleic Acid; ATP: Adenosine Triphosphate; DIC: Disseminated Intravascular Coagulation

Figure 2. Pathogenesis of sepsis, from pathogen invasion to dysregulation of immune response and shock.[16,19]

Sepsis also disrupts the resolution of inflammation. In pneumonia, inflammation typically resolves after pathogen clearance, but in sepsis, persistent immune activation and impaired efferocytosis (clearance of dead cells) lead to unresolved inflammation and tissue damage. Complement activation, particularly C5a, exacerbates neutrophil recruitment and vascular leakage.[18]

Furthermore, sepsis induces immunosuppression at later stages, characterized by reduced phagocytic function of active macrophages and increased apoptosis of immune cells like innate lymphoid cells, leaving the host vulnerable to secondary infections.[18] Excessive cytokine release also exhausts immune cells.[21] This immunosuppression leaves the host vulnerable to secondary infections and worsens outcomes.[22]

Cardiovascular dysfunction is another hallmark of sepsis, characterized by vasodilation, reduced venous return, and septic cardiomyopathy, which involves reversible depression of cardiac function due to cytokine-mediated effects on myocytes. Microvascular thrombosis and endothelial barrier disruption lead to fluid leakage, edema, and hypoperfusion, causing tissue hypoxia and lactic acidosis. Organ dysfunction arises from these combined effects, manifesting as acute respiratory distress syndrome (ARDS), acute kidney injury, hepatic dysfunction, and encephalopathy.[20]

Sepsis triggers profound disturbances in the coagulation system, characterized by uncontrolled procoagulant activation coupled with failure of physiological anticoagulant mechanisms. This imbalance reaches its most severe manifestation in disseminated intravascular coagulation (DIC), which presents the paradoxical clinical picture of simultaneous microvascular thrombosis and bleeding

diathesis.[22] The thrombotic complications arise from widespread fibrin deposition, while hemorrhagic tendencies result from consumption of clotting factors, platelets, and natural anticoagulants.[19,21]

Experimental and clinical evidence identify tissue factor (TF) as the primary initiator of coagulation activation in sepsis. Studies in both primate models and humans demonstrate that TF blockade significantly attenuates thrombin generation during endotoxemia and bacteremia. Parallel to this excessive procoagulant activity, sepsis critically impairs all major anticoagulant pathways: antithrombin levels become depleted, tissue factor pathway inhibitor (TFPI) activity is compromised, and the protein C system undergoes functional decline.[21,22]

The combination of heightened thrombin generation and diminished anticoagulant capacity creates a self-perpetuating cycle that promotes microvascular thrombosis, exacerbates endothelial injury, and ultimately contributes to multiple organ dysfunction. This coagulopathy not only reflects the severity of sepsis but also actively participates in its pathophysiology, with the degree of coagulation activation correlating with adverse clinical outcomes.[19]

A critical factor exacerbating sepsis in CAP patients is the presence of underlying conditions such as hematologic malignancies, which were associated with a 2.4-fold increased risk of bacteremia. These patients often suffer from neutropenia and mucosal barrier breakdown due to chemotherapy, allowing opportunistic pathogens to translocate into the bloodstream.[16]

The study identified *K. pneumoniae* and *E. coli* as the most common gram-negative pathogens, which evade immune clearance through mechanisms such as capsular polysaccharides and endotoxin (LPS) production, further amplifying systemic inflammation. Additionally, *S. aureus*, detected in 14.4% of bacteremic cases, can worsen sepsis through superantigens that induce toxic shock syndrome.[16]

DIAGNOSIS

The clinical manifestations of CAP are highly variable, from mild cases featuring fever, cough, and dyspnea, to severe manifestations including sepsis and respiratory failure, reflecting variations in both pathogen characteristics and host immune responses.[23,24] The first and most crucial step in managing sepsis is the early identification of patients at risk This is achieved through systematic clinical screening, especially in patients with acute conditions, using criteria such as systemic inflammatory response syndrome (SIRS), national early warning score (NEWS), modified early warning score (MEWS), or quick SOFA (qSOFA).[25]

Detection of sepsis in pneumonia begins with clinical suspicion based on symptoms such as fever, tachypnea, hypotension, and hypoxia in a patient with recent-onset respiratory symptoms and abnormal chest imaging.[26] If pneumonia is confirmed, the next step involves assessing

for organ dysfunction using scoring tools like SOFA, qSOFA, or NEWS. For instance, a NEWS score of ≥5 has been shown to trigger sepsis evaluation and empirical therapy in ICU settings effectively.[7]

According to Liengswangwong et al, these models were compared with other tools, such as MEWS and SAPS II, to assess their effectiveness in predicting early progression to septic shock among diabetic patients with pneumonia. The study found that the SOFA score had the highest predictive power, with an AUC of 0.866, and was especially useful when a score of ≥6 was applied. SOFA scores were significantly higher in patients who progressed to septic shock compared to those with sepsis alone, and were directly associated with increased mortality.[27]

The diagnosis of sepsis secondary to pneumonia requires a multifaceted approach combining clinical, laboratory, and radiological findings. Clinically, patients may present with signs of systemic infection and organ dysfunction, including hypotension (SBP <90 mmHg), altered mental status (GCS <15), respiratory failure (PaO_2/FiO_2 <300), and oliguria (<0.5 mL/kg/hr).[25]

The Sepsis 3 guidelines recommend the qSOFA criteria (RR ≥22 breaths/min, SBP ≤100 mmHg, altered mental status) for rapid sepsis risk stratification, with ≥2 criteria indicating high-risk patients requiring urgent intervention.[7,17] However, due to qSOFA's limited sensitivity (60–70%), the 2021 Surviving Sepsis Campaign advises against its use as a standalone screening tool, instead recommending adjunctive scoring systems such as NEWS or MEWS in emergency and general ward settings.[23,25] The older SIRS criteria (temperature >38°C or <36°C, HR >90 bpm, RR >20 breaths/min, WBC >12,000/μL or <4,000/μL or >10% bands) remain valuable for infection detection due to their higher sensitivity (89–96%), though they lack specificity for sepsis.[28]

The neutrophil-to-lymphocyte ratio (NLR), derived from a standard CBC, is a fast, cost-effective marker that correlates with systemic inflammation. NLR values ≥10 in patients with CAP have been associated with higher levels of C-reactive protein and inflammation, although not always directly tied to clinical severity scores. Still, its simplicity makes it useful in emergency and resource-limited settings. C-reactive protein and WBC count are also commonly elevated, but are less specific than NLR or lactate.[26]

Current biomarkers, such as procalcitonin (PCT) levels >0.5 ng/mL, suggest bacterial infection, while levels >2 ng/mL indicate sepsis risk. It helps differentiate bacterial from viral pneumonia and guide antibiotic use in CAP.[29] However, PCT can be elevated in non-infectious conditions (e.g., burns, pancreatitis) and is less reliable in VAP.[30]

C-reactive protein >50 mg/L reflects significant inflammation intensity but lacks specificity, while CRP <100 mg/L on admission correlates with lower mortality in CAP.[30] Lactate ≥2 mmol/L signals tissue hypoperfusion, and levels ≥4 mmol/L correlate with increased mortality, making serial lactate monitoring crucial for

assessing therapeutic response.[19,23] Interleukin-6 (IL-6) responds faster than CRP/PCT and predicts mortality, but has a short half-life and lacks specificity.[30]

The study by Lin et al presents a breakthrough in early sepsis detection by introducing an artificial intelligence (AI)-based model that analyzes routine blood count data to predict sepsis in patients with pneumonia. This AI model uses only the complete blood count with differential (CBC+DIFF), a test that is fast, inexpensive, and available in nearly all hospital settings.[31]

The AI algorithm, particularly the light gradient boosting machine (LGBM), processes blood cell parameters to detect complex patterns of immune dysregulation that suggest early sepsis. Among the most predictive features were the neutrophil-to-lymphocyte ratio (NLR), immature granulocyte percentage (IG%), and neutrophil side scatter (NE-SSC), all of which reflect early activation of the innate immune system in response to infection. The model achieved a high diagnostic performance, with an AUC of 0.90, and outperformed traditional scoring systems in identifying sepsis at an early stage.[31]

Chest imaging demonstrates equally variable patterns, with common radiographic features encompassing parenchymal consolidation, cavitary lesions (particularly suggestive of necrotizing infections), and parapneumonic effusions.[32] Notably, the correlation between clinical severity and radiological extent often shows significant discordance. Some patients with extensive imaging abnormalities exhibit mild symptoms, while others with limited radiographic involvement may present with profound systemic illness.[23,32]

Radiologically, chest X-rays typically reveal lobar or multilobar consolidation in bacterial pneumonia, with *Streptococcus pneumoniae* the most common CAP pathogen, often presenting as non-cavitary lobar pneumonia.[32] *Staphylococcus aureus*, more frequently associated with HAP or VAP, may demonstrate unilateral or bilateral consolidations. CT scans are reserved for suspected complications (e.g., abscess, empyema) or when initial imaging is inconclusive.[33]

Microbiological confirmation remains essential, with blood cultures positive in approximately 27.16% of severe pneumonia cases, aiding in bacteremia identification.[34] Sputum cultures and PCR testing improve pathogen detection speed (particularly for *S. pneumoniae* and *K. pneumoniae*), though cultures remain necessary for antibiotic susceptibility profiling.[35]

Emerging technologies, such as Matrix-Assisted Laser Desorption/ Ionization Time-of-Flight (MALDI-TOF) mass spectrometry and PCR-based assays, show promise for faster pathogen identification but are not yet widely adopted or fully validated.[36] This integrated diagnostic approach, combining clinical scoring, biomarkers, imaging, and microbiological testing, ensures timely sepsis recognition and guides appropriate management.

MANAGEMENT

Early Detection

Once sepsis is suspected, management must begin immediately, ideally within the first hour. Initial interventions during this critical period include obtaining blood cultures and other relevant specimens before administering antibiotics, measuring serum lactate levels, administering broad-spectrum intravenous antibiotics, and providing fluid resuscitation if signs of hypoperfusion or hypotension are present. These timely interventions are essential to improving patient outcomes and are strongly emphasized in current international guidelines.[7,25]

Antibiotic Administration

Timely and appropriate administration of antibiotics is a critical component in managing sepsis caused by pneumonia. Empiric broad-spectrum antibiotics should be initiated as soon as sepsis or septic shock is diagnosed. In patients with septic shock, antibiotics must be administered immediately, ideally within one hour, without waiting for further test results.[25]

For patients not in shock and when sepsis is uncertain, a rapid assessment should be conducted to distinguish infectious from non-infectious causes. If infection is considered possible, antibiotics should be given within three hours of recognizing sepsis. Delays in antibiotic administration are consistently linked to increased mortality, particularly in septic shock cases.[25]

The study by Yiang et al emphasizes the importance of conducting multidrug-resistant organism (MDRO) risk screening is a structured process used to identify patients at high risk of infection or colonization with drug-resistant bacteria, particularly in critical conditions like pneumonia with septic shock. This screening is essential because patients infected with MDROs such as early *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, or ESBL-producing *Enterobacteriaceae* often do not respond to standard empirical antibiotics, resulting in delayed treatment and increased mortality.[9]

The screening process involves assessing specific clinical and epidemiological risk factors within the first hour of hospital or ED admission. Key risk factors include recent hospitalization (within the past 90 days), residence in long-term care facilities or nursing homes, chronic dialysis, prior use of broad-spectrum antibiotics, recent surgery, presence of invasive medical devices (like ventilators or central lines), and a known history of MDRO colonization or infection. This proactive approach is crucial because inappropriate or delayed antibiotic treatment in MDRO-related sepsis has been consistently linked with worse outcomes, including treatment failure, prolonged ICU stay, and death.[9]

The selection of empiric antibiotics should consider the type of CAP or HAP/VAP—risk factors for resistant organisms such as MRSA and *Pseudomonas aeruginosa*, the patient's

immune status, and local epidemiology. For severe CAP, recommended regimens include a β-lactam antibiotic (e.g., ceftriaxone or ampicillin-sulbactam) combined with a macrolide (azithromycin or clarithromycin) or a fluoroquinolone (levofloxacin or moxifloxacin). For nosocomial pneumonia, empiric therapy typically involves an antipseudomonal β-lactam (such as piperacillin-tazobactam or meropenem) plus an aminoglycoside or fluoroquinolone, with the addition of anti-MRSA agents (vancomycin or linezolid) in patients with recent hospitalization and recent intravenous antibiotic use in the last 90 days.[25]

Empiric therapy should be tailored based on microbiological results and clinical response to optimize outcomes and reduce antimicrobial resistance. The balance between prompt antibiotic initiation and avoiding unnecessary exposure is essential, especially given the risks of antibiotic-related adverse effects and resistance development.

Fluid Resuscitation

Fluid resuscitation is the first and most important step in managing sepsis caused by pneumonia, aiming to improve tissue hypoperfusion and prevent multiple organ failure. Isotonic crystalloid fluids, such as 0.9% sodium chloride or Ringer's lactate, are the preferred choices due to their effectiveness and wide availability.[25]

Current guidelines recommend administering an initial minimum of 30 mL/kg of crystalloid fluid within the first three hours after diagnosis in patients presenting with hypotension or lactate levels ≥4 mmol/L. Fluids should be given rapidly with the goal of achieving a MAP of at least 65 mmHg and urine output of ≥0.5 mL/kg/hour.[25]

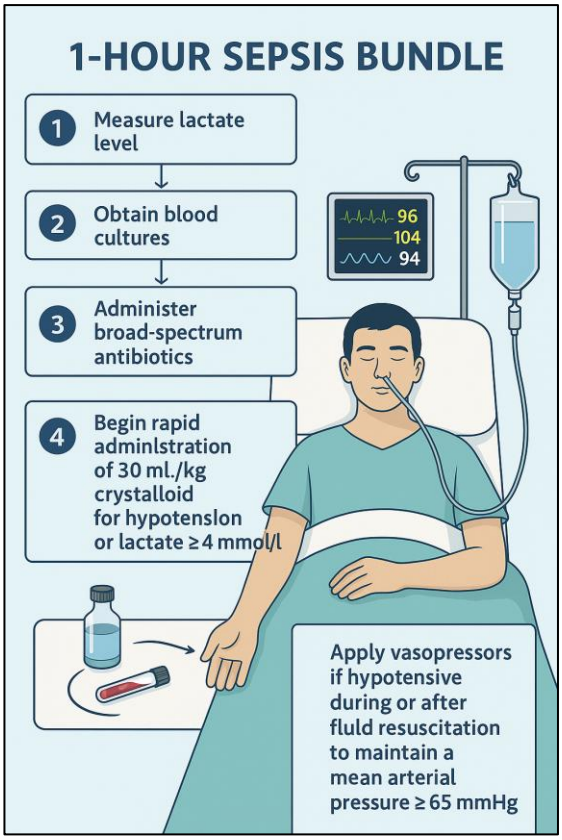


Figure 3. 1-hour sepsis bundle, lactate measurement, obtain blood culture, blood spectrum antibiotics, and fluid resuscitation.[25]

Following initial resuscitation, continuous assessment of intravascular volume status and tissue perfusion is essential to avoid fluid overload, which can exacerbate pulmonary edema, especially in patients with respiratory failure or cardiac dysfunction. Dynamic parameters such as the response to passive leg raising, pulse pressure variation, stroke volume variation, and capillary refill time monitoring can guide fluid management more effectively than static measures. Elevated blood lactate levels serve as an indirect marker of

tissue hypoperfusion and can be used as a target for ongoing resuscitation.[18]

Recent evidence suggests that while early fluid resuscitation is critical, excessive fluid administration may lead to adverse outcomes, including edema and organ dysfunction. Therefore, a balanced and individualized approach to fluid therapy, guided by hemodynamic response, is recommended to optimize patient outcomes.[25]

Organ Support

Most patients with severe sepsis or septic shock require organ support to maintain adequate organ perfusion and blood pressure. When hypotension persists despite adequate fluid resuscitation, cardiac support with vasoactive agents becomes essential. Norepinephrine is the first-line vasopressor recommended to achieve a target MAP of at least 65 mmHg. Invasive blood pressure monitoring, such as via an arterial line, is advised for accurate and continuous monitoring in patients with shock.[25]

If central venous access is not yet established, vasopressors may be administered peripherally but only for a short duration through a large proximal vein (e.g., antecubital vein) with careful monitoring to avoid complications. Vasopressin can be added as an adjunct if the MAP target is not reached despite low to moderate doses of norepinephrine. In cases of cardiac dysfunction with persistent hypoperfusion despite adequate volume status and blood pressure, dobutamine may be added or norepinephrine replaced with epinephrine. Early initiation of norepinephrine, preferably within the first hour of septic shock diagnosis, has been shown to improve hemodynamic outcomes, reduce the duration of hypotension, and potentially decrease fluid overload and associated complications.[1,2]

Severe pneumonia causes respiratory dysfunction, which may lead to acute respiratory failure. Supplemental oxygen should be provided to maintain oxygen saturation (SpO_2) ≥92%. If severe hypoxemia or increased work of breathing occurs, non-invasive ventilation or invasive mechanical ventilation (intubation) should be considered. Regular assessment and monitoring of other organ functions, including renal, hepatic, and coagulation systems, are necessary to detect and manage multiple organ dysfunction syndrome (MODS). A comprehensive organ support approach is critical to improving survival in patients with severe sepsis or septic shock.[25]

Corticosteroid

Corticosteroids play a complex yet significant role in sepsis management, particularly in patients with septic shock who are unresponsive to fluids and vasopressors. Recent systematic reviews and meta-analyses within the last decade demonstrate that corticosteroids, especially hydrocortisone at moderate doses (260 mg/day or equivalent), are effective in improving shock reversal and reducing short-term mortality in septic patients.[37]

These benefits are primarily attributed to the anti-inflammatory

properties of corticosteroids, which help modulate the overwhelming immune response and reduce organ dysfunction by downregulating pro-inflammatory cytokines. Additionally, corticosteroids improve cardiovascular stability by restoring effective blood volume and increasing systemic vascular resistance through glucocorticoid receptor-mediated mechanisms.[37,38]

However, corticosteroid therapy could increase incidences of hyperglycemia, hypernatremia, and neuromuscular weakness. Despite these adverse effects, corticosteroids remain a conditional recommendation in guidelines for patients with septic shock requiring vasopressor support.[37,38]

PROGNOSIS

Sepsis is a life-threatening condition with a high mortality rate. Globally, it is estimated that between one in three to one in six patients with sepsis or septic shock die despite receiving treatment. Early recognition and appropriate management within the first few hours of sepsis onset can significantly improve prognosis. However, even after surviving the acute phase, many patients face prolonged and complex recoveries, with long-term complications and rehabilitation needs posing major challenges.[1,25]

In Indonesia, sepsis mortality rates vary widely, ranging from approximately 24% to as high as 65%, with some studies reporting sepsis mortality around 30% and septic shock mortality reaching up to 80%. Factors contributing to these high mortality rates include delayed treatment, a high burden of comorbidities such as diabetes and the severity of organ dysfunction. Hospital-acquired pneumonia is a common infectious cause associated with increased mortality risk.[1,2]

Early and comprehensive management, especially prompt antibiotic administration and organ support, has been shown to reduce mortality significantly. Despite advances in care, sepsis remains a major global health problem, particularly in low- and middle-income countries, where it contributes to millions of deaths annually.[25]

CONCLUSION

Sepsis secondary to pneumonia remains a life-threatening condition with persistently high mortality rates, necessitating urgent recognition and intervention. The complex interplay of immune dysregulation, endothelial dysfunction, and coagulation abnormalities requires a multifaceted management approach centered on early diagnosis through clinical scoring systems and biomarkers, followed by immediate antimicrobial therapy and hemodynamic stabilization.

The implementation of the "1-hour bundle" protocol, emphasizing rapid antibiotic administration, fluid resuscitation, and vasopressor support when needed, has significantly improved clinical outcomes. However, challenges remain in resource-limited settings and cases involving

resistant pathogens. Moving forward, the development of advanced diagnostic tools like AI-based models, enhanced antimicrobial stewardship programs, and comprehensive post-sepsis rehabilitation protocols will be critical to addressing both acute management and long-term recovery.

By combining evidence-based practices with technological innovations and personalized treatment strategies, healthcare systems can reduce the global impact of pneumonia-associated sepsis and improve both survival rates and quality of life for survivors, while ongoing research should continue to refine diagnostic accuracy and therapeutic approaches for this complex condition.

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