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Sepsis in Respiratory Diseases: A Narrative Review

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Abstract: **Objective:** To review the epidemiology, clinical spectrum, and management of sepsis in respiratory diseases, with emphasis on implications for clinical practice. **Design:** Narrative review. **Data sources:** PubMed, Google Scholar, and international guideline documents including the Surviving Sepsis Campaign. **Eligibility criteria:** English-language studies, reviews, and guidelines addressing adult sepsis and respiratory infections. **Results:** Respiratory infections are the leading source of sepsis and are associated with the highest mortality. Patients with pneumonia, chronic obstructive pulmonary disease, Tuberculosis, interstitial lung disease, and malignancy are at particularly high risk. Early identification and prompt implementation of evidence-based management bundles are associated with improved outcomes. **Conclusions:** Sepsis remains a major contributor to mortality among patients with respiratory diseases. Standardised recognition, timely management, and preventive strategies are essential to improve outcomes.

Keywords: Sepsis, Septic Shock, Respiratory Diseases, Pneumonia, Tuberculosis

INTRODUCTION

Sepsis and septic shock remain among the most important causes of morbidity and mortality in hospitalised patients worldwide. Understanding the global and local burden of sepsis is fundamental to designing strategies that reduce its clinical and economic impact. Although most epidemiological data originate from high-income countries, recent estimates indicate that low- and middle-income countries account for the majority of sepsis-related deaths. Respiratory infections are the leading source of sepsis and contribute disproportionately to mortality, making sepsis a critical concern in respiratory medicine practice

WHO, in recognition of the importance of this problem, made sepsis a global health priority in 2017 and urged the need to implement measures to reduce the human and catastrophic economic costs due to sepsis.

Early identification and management of sepsis is the key to addressing the morbidity, mortality, and economic catastrophic costs due to sepsis.

METHODS

This narrative review synthesizes evidence from published epidemiological studies, observational cohorts, clinical trials, and international guidelines relevant to sepsis and respiratory diseases. Databases searched included PubMed and Google Scholar. Priority was given to recent studies, landmark consensus definitions, and guideline documents. The review focuses on adult patients and integrates global and Indian data where available.

EPIDEMIOLOGY OF SEPSIS IN RESPIRATORY DISEASES

Sepsis and septic shock are among the leading causes of critical care admissions and mortality in hospitalised patients globally. The estimated incidence in the United States is 300 per one lakh population, with one-fourth of patients with sepsis and half of the patients with septic shock dying during hospitalisation, which highlights the public health importance of this problem (1).

Most epidemiological data available are from high-income countries, and the global burden of disease estimated that in 2017, there were 48.9 million sepsis cases and 11 million deaths (19.7 % of global deaths) in that year. As with other health problems, the highest burden, however, is in the low- and middle-income countries, which account for 85 % of these deaths. In India, the estimates were 11.3 million cases with 2.9 million deaths (297.7 per one lakh population) (2,3).

Table 1: The global and Indian prevalence of sepsis and its mortality (2017 Data)

	Global	**India**
Incidence of sepsis	48.9 Million cases	11.3 Million cases
Mortality due to sepsis	11 million deaths	2.9 million deaths

Analysis of mortality patterns among patients who died in the Department of Respiratory Medicine of Madras Medical College in 2024 showed that sepsis and septic shock accounted for 45 % of these patients, which highlights the fact that it is still a major public health problem in our country. This is consistent with the reported sepsis prevalence in India of 46.2% using the sepsis-2 definition, 33.2% using the sepsis-3 definition, and 56.4% using either definition (2,3).

DEFINITIONS OF SEPSIS AND SEPTIC SHOCK

There have been changes in the definition of sepsis over time. The 1991 consensus statement defined sepsis as systemic inflammatory response syndrome (SIRS) to infection. In 2001, Sepsis-2 was defined as two or more SIRS criteria and infection on the same day. If less than two SIRS criteria or if the infection resolved, the patient was no longer regarded as septic. The current consensus document describes Sepsis-3, which was defined as an increase in Sequential Organ Failure Assessment (SOFA) score of two or more in conjunction with an infection (4).

Table 2: The changing definition of sepsis

DEFINITIONS	SEPSIS – 1 (1991)	Sepsis – 2 (2001)	Sepsis – 3 (2016)
Sepsis	Systemic response to infection manifested by 2 or more of SIRS criteria as a result of infection	Same definitions as Sepsis-1 with greater number & detail of signs and symptoms	A life threatening organ dysfunction caused by dysregulated host response to infection Suspected or documented infection & increase SOFA >2
Severe Sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension	Same definitions as Sepsis-1 with greater number & detail of signs and symptoms	No longer applicable
Septic shock	Sepsis-induced, wit hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities	Same definitions as Sepsis-1 with greater number & detail of signs and symptoms	Can be identified with a clinical construct of sepsis with persistent hypotension, requiring vasopressor therapy to elevate MAP to 65 mm Hg despite adequate fluid resuscitation

DEFINING SEPSIS AND SEPTIC SHOCK

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For practical considerations, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. (5)

The qSOFA (Quick SOFA) score identifies high-risk patients for in-hospital mortality. It is used for patients ≥ 18 years old in a non-ICU setting with suspected sepsis. It's a simple score using only 3 clinical parameters – altered mental status, respiratory rate, and systolic blood pressure.

Table 3: qSOFA score and its interpretation.

qSOFA scoring and Interpretation		
Parameter	0 Points	1 point
Altered mental status GCS < 15	No	Yes
Respiratory Rate ≥ 22	No	Yes
Systolic BP≤ 100	No	Yes
Interpretation of the qSOFA score		
QSOFA SCORE	RISK GROUP	
1	No risk for in-hospital mortality	
2 - 3	High risk for in-hospital mortality	

Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

A patient is diagnosed with **septic shock** if they have:

1. **Sepsis** (confirmed infection with organ dysfunction, often measured using SOFA score).
2. **Persistent Hypotension** requiring vasopressors to maintain **Mean Arterial Pressure (MAP) ≥ 65 mmHg**.
3. **Serum Lactate > 2 mmol/L** (>18 mg/dL) despite adequate fluid resuscitation, indicating impaired tissue perfusion.

   This combination is associated with hospital mortality rates greater than 40% (5)

SOURCES, RISK FACTORS, AND MICROBES LEADING TO SEPSIS

Respiratory infections are the most common source of sepsis and occur in one-third of all cases of sepsis. Pneumonias also account for the highest mortality in sepsis. Other sources include genitourinary tract, abdominal, wound, and soft tissue infections, device-related, endocarditis, and bacteraemia of unknown source (6,7).

Table 4: Sources of Sepsis

Sources of Sepsis	Examples of infections
Lung	Pneumonia, ARDS, Viral infections like COVID-19 and influenza, Suppurative lung diseases
Urinary Tract	UTI and Pyelonephritis
Abdomen	Cholecystitis, Peritonitis
Skin and soft tissues	Cellulitis, bedsores, necrotizing fasciitis
Bloodstream infections	Catheter-induced, endocarditis
Central nervous system	Meningitis, Brain abscess
Others	Immunocompromised, post-surgical sites

Risk factors for sepsis include age > 65 years, male gender, low socioeconomic status, and patients with chronic health conditions like diabetes, chronic obstructive pulmonary disease, cancer, and chronic renal and liver disease. Other risk factors include staying in long-term care facilities, recent surgery or mechanical ventilation, smoking, exposure to environmental pollutants, malnutrition, and immunosuppressive therapy. (6,7) In the Indian context, among patients with sepsis, bacterial infections were most common (77.9%) with the majority being gram-negative bacteria, followed by fungal infections (9.6%). Multidrug-resistant infections were present in 44.8% of patients with sepsis. (2,3)

PATHOPHYSIOLOGY OF SEPSIS IN RESPIRATORY DISEASES

Respiratory infections like pneumonias trigger sepsis by the release of pro-inflammatory cytokines, leading to widespread inflammation, which can impair blood flow to organs and cause tissue damage and organ dysfunction in organs like the kidneys, liver, and the heart. Septic shock leads to multiorgan dysfunction by affecting the tissue perfusion to various organs.

SEPSIS IN RESPIRATORY DISEASES

In patients admitted to the respiratory medicine department, sepsis is encountered both at admission and during the hospital stay. Common scenarios of patients admitted with sepsis from the respiratory tract include patients with pneumonia with sepsis, COPD patients, Tuberculous patients, and patients with lung malignancies, especially on chemotherapy. Not infrequently, sepsis from upper respiratory infections like purulent sinusitis is also encountered and needs to be looked for. The respiratory system can also be involved due to sepsis, which originates from other systems such as urosepsis, sepsis from infected skin lesions like cellulitis or bed sores, catheter-associated infections, etc.

As mentioned earlier, pneumonias account for a high burden of mortality due to sepsis. Pneumonias usually occur in immunosuppressed patients, and bacteraemia leading to sepsis and septic shock is commonly encountered in these patients. Various scoring systems like the CURB-65, Pneumonia Severity Index have been developed for earlier identification and triage of these patients so that early treatment can be initiated and mortality reduced. (8). In addition, suppurative lung diseases including bronchiectasis, lung abscess, empyema, and necrotising pneumonias may also lead to sepsis.

In COPD patients, sepsis is a common association, and infective exacerbations can lead to bloodstream dissemination of organisms and subsequent sepsis and septic shock. Sepsis accounts for a high burden of mortality among COPD patients. COPD patients are immunosuppressed due to chronic use of steroids and frequently land with sepsis. On the other hand, sepsis due to infection from other sites also leads to worsening of preexisting COPD, adding to the disease burden. COPD patients also have other comorbidities like Diabetes, coronary artery disease, smoking, alcoholism, and malignancies, which also increase the risk of sepsis in these patients. (9)

Interstitial lung disease patients are also prone to sepsis due to their lowered local lung immunity and also due to the widespread use of steroids and immunosuppressive therapies in the management of these patients.

In our country, Tuberculosis is rampant, and very often we encounter patients with Tuberculosis admitted with sepsis. The already infected Tuberculous lung is also prone to secondary infections, including bacterial, especially gram-negative bacteria, fungal, and viral infections, and leads to a multiplication of woes for the patient. Also, 30 % of these patients are diabetics and immunocompromised. HIV TB coinfection is also another common coinfection. Smoking, Alcoholism, and malnutrition are other associations, and sepsis is multifactorial in these patients due to a combination of host, agent, and environmental factors. Tuberculous Mycobacteremia can also lead to sepsis and is rarely encountered, especially in immunosuppressed patients like people living with HIV/AIDS and in diabetics. (10)

Among our admissions to the pulmonology department are also malignancies, including lung malignancies, which present with sepsis. Malignancy patients are immunosuppressed due to the disease, and the treatment of malignancies with chemotherapy, radiotherapy, and biologicals adds to the immunosuppression, which leads to leukopenia and neutropenia and subsequent infection leading to sepsis and septic shock due to various microbes, including bacterial and fungal. Sepsis in these cases is due to an

interplay of an immunosuppressed host, virulent microbes, and environmental factors like prolonged hospital stay and frequent hospital visits. (11)

While speaking of the respiratory tract, sepsis due to sources from the upper respiratory tract, especially the paranasal sinuses, also needs to be considered. The author has encountered a sepsis in a traffic accident patient with facial injuries, where a prolonged search for the source of sepsis ultimately led to a purulent maxillary sinus infection of a hematoma there and drainage of the pus collected in the maxillary sinus was required to control the sepsis.

Often, we encounter patients admitted to the pulmonology ward for reasons like bronchitis, pneumonia, who have sepsis from a distant source. One of the commonest causes is urosepsis, which is frequently encountered in Diabetics, patients with chronic kidney disease, females, and elderly males due to enlargement of the prostate. Hence, it is prudent to always look for an infectious source in the genitourinary tract in all patients with sepsis, both as a causation and a correlation, since earlier detection and management of the same could alter the course and outcome of the patient.

Patients on long stay in respiratory ICU and wards and bedridden patients develop sepsis from sources including lungs (hypostatic and aspiration pneumonias), genitourinary tract, bed sores, and various catheter-associated infections including IV lines, Foley's catheter, etc. With the increasing prevalence of solid organ transplants, this is another cohort of patients who have a significantly increased incidence of sepsis. Challenges in this group include diminished clinical symptoms like fever and attenuated leucocytosis and radiological findings. The management of sepsis in this group follows the general guidelines for other patients (12). ARDS and acute lung injury (ALI) can be a consequence of sepsis, and conversely, ARDS and ALI due to any cause can also lead to the development of sepsis.

Not infrequently, patients with respiratory distress are admitted to pulmonology wards, only to be found to have metabolic acidosis and Kussmaul acidotic breathing with deep, rapid breaths, the cause of acidosis being sepsis or conditions like diabetic keto acidosis.

Table 5: Sources of sepsis from the respiratory tract and the common pathogens

Respiratory Condition	Common Pathogens	Description
Bacterial Pneumonia	*Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Haemophilus influenzae*	Infection in the lungs leading to inflammation and fluid buildup.
Viral Pneumonia	*Influenza virus*, *SARS-CoV-2 (COVID-19)*, *RSV*	Viral infection causing lung inflammation and impaired oxygen exchange.
Aspiration Pneumonia	*Anaerobes*, *Staphylococcus aureus*, *Gram-negative bacteria*	Infection due to inhalation of food, liquids, or stomach contents into the lungs.
Tuberculosis (TB) Infection	*Mycobacterium tuberculosis*	Chronic bacterial lung infection that can progress to systemic sepsis.

Lung Abscess	*Staphylococcus aureus*, *Bacteroides*, *Fusobacterium*	Localized pus collection in the lung tissue leading to severe infection.
Empyema (Pus in Pleural Space)	*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Gram-negative rods*	Infection of the pleural space, often as a complication of pneumonia.
COVID-19-related Sepsis	*SARS-CoV-2*	Severe viral pneumonia leading to cytokine storm and multi-organ failure.
Bronchiectasis with Infection	*Pseudomonas aeruginosa*, *Haemophilus influenzae*	Chronic lung damage with recurrent infections leading to sepsis.

MANAGEMENT OF SEPSIS AND SEPTIC SHOCK IN RESPIRATORY DISEASES

Early diagnosis and management are the key to saving lives in sepsis and identification of sepsis in respiratory disease involves identifying clinical signs like fever, increased heart rate and low blood pressure, blood investigations like elevated white cell count, positive cultures for bacteria and elevated inflammatory markers like C reactive protein, and imaging like chest radiograph or CT chest to assess lung involvement and the extent of infection.

Surviving sepsis campaign guidelines, last updated in 2021(13) provides guidance to clinicians on management of sepsis with the goal of reducing the mortality due to sepsis. Sepsis screening for acutely ill and high-risk patients and a standardised treatment protocol has been strongly recommended in the guidelines.

Various clinical parameters and screening tools have been recommended in the guidelines including systemic inflammatory response syndrome (SIRS) criteria, vital signs, signs of infection, quick Sequential Organ Failure Score (qSOFA) or Sequential Organ Failure Assessment (SOFA) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS).

The qSOFA is a simple screening tool that uses three variables to predict death and prolonged ICU stay in patients with known or suspected sepsis: a Glasgow Coma Score < 15, a respiratory rate ≥ 22 breaths/min, and a systolic blood pressure ≤ 100 mm Hg. When any two of these variables are present simultaneously, the patient is considered qSOFA positive. However, this system has a low sensitivity for sepsis, and the guidelines do not recommend use of this as a single screening tool for sepsis.

Standard operating procedures are a set of practices that specify a preferred response to specific clinical circumstances. Sepsis standard operating procedures include a standard approach with components of the sepsis bundle, early identification, lactate, cultures, antibiotics, and fluids

The “sepsis bundle” has been the keystone of improving survival in the Surviving Sepsis Campaign, and currently, the one-hour bundle is in vogue. It includes measuring lactate level, obtaining blood cultures before starting antibiotics, administering broad-spectrum antibiotics, rapid administration of 30 ml per kg crystalloids for hypotension or if lactate is ≥ 4 mmol/L, and applying vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain a mean arterial pressure of ≥ 65 mm Hg. It is imperative to note that Serum lactate is a surrogate and not a direct marker of tissue perfusion and the

increase may be due to tissue hypoxia, accelerated aerobic glycolysis, and other organ failure like the liver. Standardized lab measurements are available and randomized control trials show that lactate-guided resuscitation leads to lower mortality.

Mean arterial pressure is the driving pressure for tissue perfusion, and the target is fixed at 65 to minimize the risk of cardiac arrhythmias, lower the dose of vasopressors, and reduce mortality. Below this threshold, the tissue perfusion is linearly dependent on arterial pressure.

Usually, Noradrenaline is the first choice of inotrope, and adrenaline is used when an additional agent is needed. Vasopressin is added as a salvage therapy with the intent of raising mean arterial pressure or decreasing the dose of Noradrenaline. Dopamine is used in selected patients with a low risk of tachycardia or relative absolute bradycardia. Noradrenaline is the first choice because of its vasoconstrictive effect in sepsis without increasing heart rate and stroke volume compared to Dopamine. Dopamine has arrhythmogenic potential and has an immunosuppressive effect on the hypothalamic-pituitary axis. Steroid therapy with hydrocortisone 200 mgs per day is used in cases where the MAP cannot be maintained ≥ 65 mm Hg despite adequate fluid and inotrope therapy.

Regarding antimicrobial therapy, it should be started within the first hour of recognizing sepsis or septic shock and the regimen should be monitored daily to assess for possible de-escalation. Usually, a combination of beta-lactam with macrolide is used, but prudence dictates that the choice be dictated by the prevailing antimicrobial policy of the institution. Procalcitonin is a biomarker that assists in discontinuing antibiotics in patients who initially appear septic.

Combination antibiotic therapy is needed in patients with neutropenia, severe sepsis, or difficult-to-treat sepsis and in patients with multidrug-resistant organisms like Acinetobacter and Pseudomonas. Usually, in such cases, a combination of beta-lactam and aminoglycosides/ fluoroquinolone is used.

As a policy, empirical antibiotics should not be continued beyond three to five days, and efforts should be taken to identify the microbe and change to a single-guided therapy as soon as possible.

Antifungals are used in selected situations where there is a high suspicion of fungal sepsis, such as in febrile neutropenia, organ transplant, and people living with HIV/AIDS.

The surviving sepsis guidelines make no recommendation for antivirals in sepsis due to the risk of undesirable side effects and lack of data on cost-effectiveness.

Efforts to address the source of infection and to remove the source like infected wounds or catheters, should also be done.

Other supportive measures advocated in the management of patients with sepsis include infection prevention measures like limited patient contact and hand washing, use of blood products like pRBC for anaemia correction and Fresh frozen plasma for coagulopathies, mechanical ventilation for sepsis induced ARDS, glucose control, bicarbonate correction if pH ≤ 7.15, DVT and stress ulcer prophylaxis and ensuring adequate nutrition for the patients.

PREVENTING SEPSIS – THE WAY FORWARD

The first major hurdle to cross as far as preventing sepsis is concerned is to understand the epidemiology of sepsis in the Indian scenario. There is a wide variation in the prevalence, the aetiology, and the microbes causing sepsis in various health care facilities, and the treating physician should be aware of these factors and the local antibiograms for effectively treating and preventing sepsis, and also to address the issues of emerging antimicrobial resistance in the future.

Surveillance for infections like the COVID pandemic and the recurring flu pandemics, and prevention of nosocomial infections by appropriate measures like hand washing, contact isolation, use of personal protective equipment and early identification of infections including catheter associated infections and use of appropriate antibiotics are needed.

Health care workers need to be trained regarding the causation of sepsis, symptoms and signs and preventive aspects of sepsis.

Policy level changes including health education, early health seeking behaviour, improvement in air and water quality, hygiene measures like cough hygiene and hand washing need to be advocated.

Control and prevention of chronic illnesses like Diabetes, COPD, HIV, and vaccination for preventable diseases like pneumonias with pneumococcal and influenza are also a need of the hour to reduce the morbidity, mortality, and economic burden of sepsis in respiratory diseases.

CONCLUSION

Sepsis remains a major and preventable contributor to mortality in patients with respiratory diseases, particularly in low- and middle-income countries such as India. Respiratory infections—including pneumonia, tuberculosis, COPD exacerbations, malignancy-related infections, and hospital-acquired infections—are the predominant sources and are frequently complicated by delayed recognition and antimicrobial resistance. Early identification, prompt implementation of evidence-based sepsis bundles, rational antimicrobial use, and timely source control are central to improving outcomes. Strengthening surveillance, infection prevention, vaccination, chronic disease control, and healthcare worker training is essential to reducing the overall burden of sepsis in respiratory medicine.

DECLARATIONS

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