SEPSIS

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis can be caused by various types of infections, including bacterial, viral, fungal, or parasitic and can affect people of all ages.

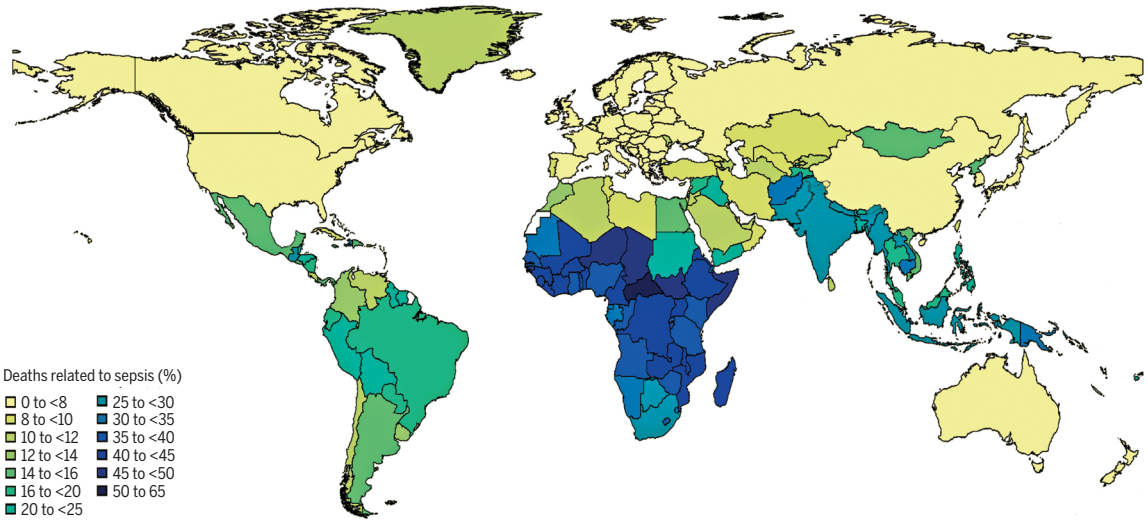
Septic shock is a subset of sepsis, characterized by a critical reduction in tissue perfusion, where acute failure of multiple organs (such as lungs, kidneys, etc.) can occur. Septic shock is associated with a higher risk of mortality compared to sepsis alone.

BURDEN AND EPIDEMIOLOGY

- **Burden of sepsis:** In 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths. Almost half of all global sepsis cases occurred among children, with an estimated 20 million cases and 2.9 million global deaths in children under 5 years of age.[2]
- **Economic burden:** Sepsis places a significant economic burden on healthcare systems due to prolonged hospitalizations, intensive care unit (ICU) admissions, and the need for expensive treatments and interventions.
- **Mortality rate:** Sepsis is associated with a high mortality rate, especially in severe cases. Mortality rates can range from 10% in mild cases to over 40% in cases of septic shock.[3] Early recognition and appropriate treatment are essential for improving outcomes.
- **Global impact:** Sepsis has a substantial global impact, with varying rates in different regions. Low- and middle-income countries may face unique challenges in sepsis diagnosis and management due to limited resources. Approximately 85% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries.[2]

Figure 1. Percentage of all deaths related to sepsis, age-standardised for both sexes, in 2017

Rudd K E, *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet 2020; 395:100-11.



CLINICAL PRESENTATION

SIGNS AND SYMPTOMS OF SEPSIS


Shivering, fever, or very cold


Extreme pain or discomfort


Clammy or sweaty skin


Confusion or disorientation


Shortness of breath


Increased heart rate

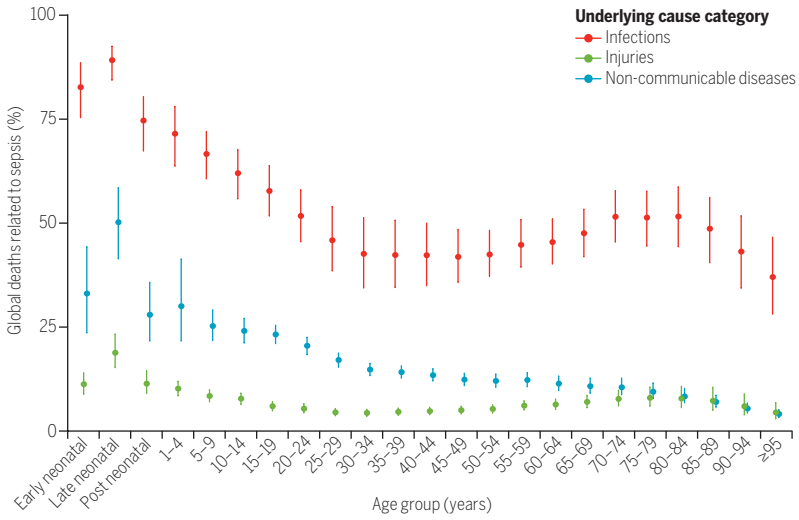
PATHOPHYSIOLOGY OF SEPSIS [4]

- Sepsis is characterized by an overwhelming release of inflammatory mediators, in response to an infection.
- During the immune response to infection, the body's defenses recruit and activate, circulating immune cells such as NK cells, dendritic cells, platelets, monocytes and eosinophils, at the site of infection. The Pathogen Recognition Receptors (PRRs) on the surface of these cells can detect Pathogen-Associated or Damage-Associated Molecular Patterns (PAMPs or DAMPs) on the surface of the pathogen. This interaction initiates intracellular signaling and an immuno-inflammatory cascade, including cytokine release, that may lead to a "**cytokine storm**".
- Additionally, a compensatory anti-inflammatory response can become dysregulated, leading to an imbalance between pro- and anti-inflammatory processes and the development of an **immunosuppression** that may contribute to **organ damage**.

CAUSES OF SEPSIS

Figure 2. Percentage of all sepsis-related deaths in each underlying cause category, by age group and for both sexes, in 2017

Rudd K E, *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet 2020; 395:100-11.



Among bloodstream infections, the most frequent pathogens causing sepsis worldwide are ***Staphylococcus aureus*** and ***Escherichia coli*** [5]

Bacterial infection is the primary cause of sepsis.

More than 75% of deaths observed in neonatal groups were due to sepsis.

Figure 3. Common infections can lead to sepsis [6]

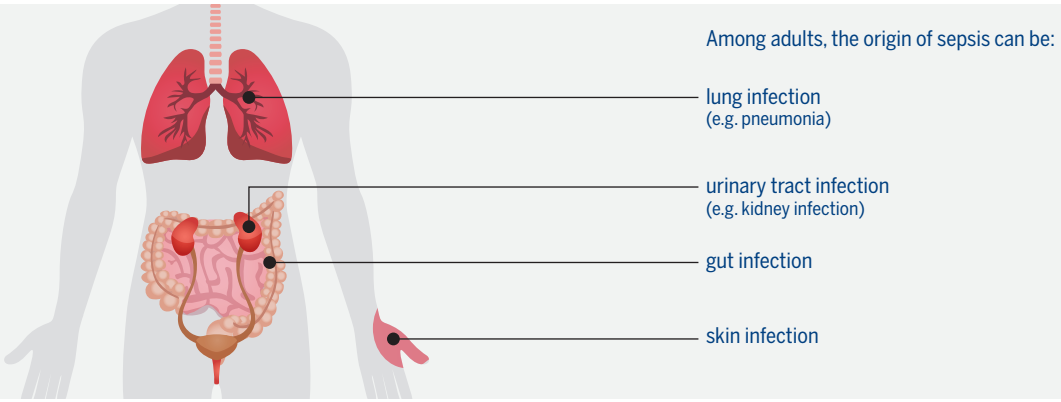


Table 1. Rank order and frequency of most common organisms causing bloodstream infections in the 1997-2000 and 2013-2016 time periods stratified by region

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Rank[a]	Frequency of species in the first (1997–2000) and last (2013–2016) time periods for:			
	North America (% during 1997–2000, % during 2013–2016)	**Latin America** (% during 1997–2000, % during 2013–2016)	**Europe** (% during 1997–2000, % during 2013–2016)	**Asia-Pacific** (% during 1997–2000, % during 2013–2016)
1	*S. aureus* (25.3, 24.3)	*E. coli* (17.2, 18.3)	*E. coli* (21.0, 27.0)	*E. coli* (21.6, 33.7)
2	*E. coli* (17.5, 19.8)	*S. aureus* (21.5, 16.4)	*S. aureus* (18.2, 16.9)	*S. aureus* (20.8, 13.9)
3	*K. pneumoniae* (6.5, 8.6)	*K. pneumoniae* (9.2, 13.6)	*K. pneumoniae* (5.8, 10.1)	*K. pneumoniae* (7.6, 13.5)
4	*E. faecalis* (6.2, 5.4)	*P. aeruginosa* (6.5, 7.1)	*P. aeruginosa* (5.9, 5.8)	*P. aeruginosa* (4.8, 5.7)
5	*P. aeruginosa* (4.5, 4.8)	*E. cloacae* (3.6, 5.9)	*E. faecalis* (4.6, 5.4)	*E. cloacae* (3.4, 3.0)
6	*S. epidermidis* (3.3, 4.6)	*A. baumannii*[b] (3.2, 5.5)	*S. epidermidis* (7.8, 4.1)	*E. faecalis* (3.4, 2.9)
7	*E. faecium* (2.3, 3.4)	*S. epidermidis* (4.6, 5.4)	*E. faecium* (1.5, 4.0)	*A. baumannii*[b] (2.1, 2.7)
8	*E. cloacae* (2.8, 3.1)	*E. faecalis* (2.2, 5.0)	*E. cloacae* (2.7, 2.6)	*E. faecium* (1.1, 2.6)
9	*S. pneumoniae* (4.8, 2.4)	*S. marcescens* (1.5, 3.3)	*A. baumannii*[b] (1.8, 2.4)	*S. epidermidis* (4.8, 2.5)
10	*S. agalactiae* (2.0, 2.2)	*E. faecium* (0.3, 2.4)	*P. mirabilis* (1.8, 2.3)	*S. agalactiae* (1.2, 1.9)

[a]Rank order based on the 2013-to-2016 time period.
[b]*Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex.

RISK FACTORS [2]

- **Ages:** Advanced age is associated with a poorer prognosis in sepsis. Elderly and young individuals often have weaker immune systems and may have multiple comorbidities, making it harder for them to combat the infection.
- **Underlying conditions:** Preexisting conditions, such as diabetes, cancer, chronic lung diseases, people without spleen and immunosuppression, are a risk factor of developing sepsis. These conditions can significantly impact prognosis and weaken the body's ability to fight infections.
- **Nosocomial sepsis:** Hospital-acquired or nosocomial sepsis is a significant concern. Infections acquired during hospital stays, especially in ICUs, can lead to sepsis. Effective infection prevention and control practices are crucial to reduce nosocomial sepsis.

SEPSIS PROGRESSION

Infection
Sepsis typically begins with an infection caused by bacteria, viruses, fungi, or parasites. This infection can occur anywhere in the body.

Dysregulated Immune Response
In sepsis, the body's immune system responds to the infection in an abnormal and harmful way. Instead of effectively fighting off the infection, the immune response triggers an excessive inflammatory reaction.

Systemic Inflammation
The inflammatory response in sepsis is not limited to the site of the infection but spreads throughout the bloodstream. This can lead to widespread inflammation and affect multiple organs and systems.

Organ Dysfunction
As a result of the systemic inflammation, organs may not function properly. This can lead to a range of symptoms and complications such as organ failure.

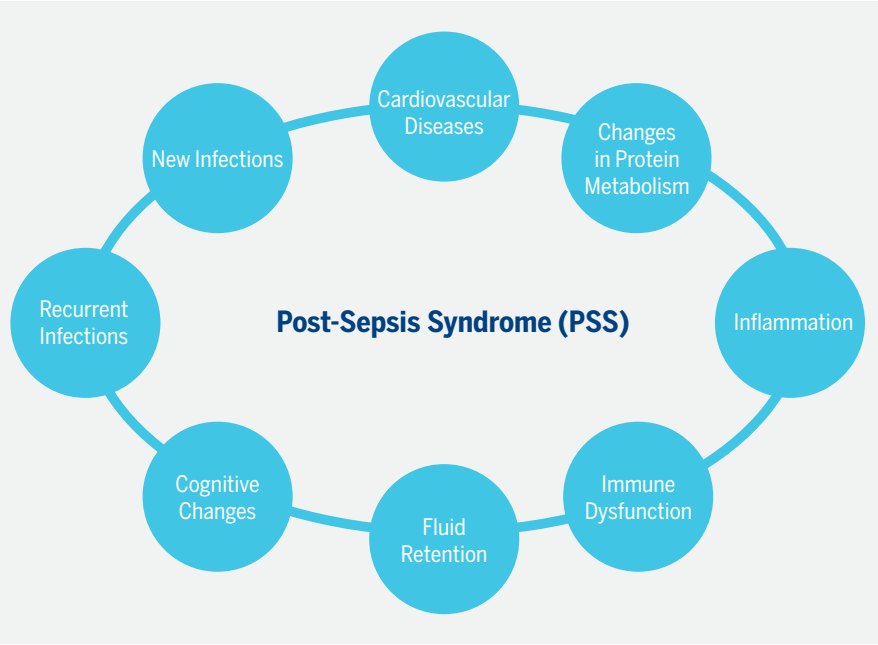
Not all bacteremia lead to sepsis

LONG-TERM CONSEQUENCES

Survivors of sepsis may experience long-term physical and psychological effects, a condition known as **Post-Sepsis Syndrome** (PSS).

These effects can include:

- Cognitive impairment
- Physical disabilities
- Mental health issues



Reproduced with permission from Gritte R, *et al.*, Why Septic Patients Remain Sick After Hospital Discharge? Front Immunol. 2021; 11:605666.

PATIENT MANAGEMENT

In addition to fluid resuscitation and hemodynamic monitoring (or "vasoactive drug monitoring") (refer to guidelines), appropriate patient management includes:

1 Severity assessment [7][8]

Several sepsis screening tools aim to facilitate early identification of sepsis, employing either manual methods or automated integration with electronic health records (EHR). Common screening variables include:

SOFA (Sequential Organ Failure Assessment):
- respiratory rate
- coagulation
- liver
- cardiovascular
- central nervous system
- renal systems

qSOFA* (quick Sequential Organ Failure Assessment):
- respiratory rate
- systolic blood pressure
- Glasgow Coma Score (GCS)

SIRS (Systemic Inflammatory Response Syndrome):
- temperature
- respiratory rate
- heart rate
- white blood cell count

NEWS (National Early Warning Score):
- temperature
- respiratory rate
- heart rate
- systolic blood pressure
- oxygen saturation
- level of consciousness
- oxygen saturation on room air (NEWS2)

MEWS (Modified Early Warning Score):
- respiratory rate
- heart rate
- systolic blood pressure

Numerous studies have produced contradictory results on the usefulness of these tools, showing that qSOFA is more specific but less sensitive than SIRS criteria for early identification of infection-induced organ dysfunction. [10]

*** In 2021, Surviving Sepsis Campaign guidelines strongly recommend against using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock. [10]**

2 Pathogen identification

- Blood cultures
- Gram stain to **identify** broad category of pathogen
- Polymerase Chain Reaction (PCR) testing for **rapid pathogen identification** (ID) and detection of selected **genotypic antimicrobial resistance markers**
- MALDI-TOF or other automated identification testing on pathogen recovered from positive blood culture
- Antimicrobial Susceptibility Testing (AST) to determine the **phenotypic antimicrobial resistance** of the pathogen

3 Imaging

- X-ray
- Ultrasound
- Computed Tomography (CT) scan

4 Treatment monitoring

Inflammatory biomarkers: like C-reactive protein (CRP) and Procalcitonin (PCT) can be elevated in sepsis and may be used to monitor the inflammatory response to treatment.

Antimicrobial treatment (2021 SSC guidelines)

Sepsis not confirmed without shock

Antibiotic treatment within
3 hours
after patient admission in ED

Sepsis confirmed with or without shock

Antibiotic treatment within
1 hour
after patient admission in ED

Of the 67% patient receiving empiric broad spectrum antibiotics; 13.6% had gram-positive resistant organisms and 13.2 % had gram-negative resistant organisms. [9]

GUIDELINES AND KEY RESOURCES

It's important to note that guidelines can vary by region and organization, the ones mentioned below are considered key references for healthcare professionals.

- **Surviving Sepsis Campaign (SSC) | Society of Critical Care Medecine (SCCM)** [10]
- **Pediatric Sepsis Guidelines** [11]
- **JAMA Network** [12]
- **WHO sepsis** [13]
- **Global Sepsis Alliance** [14]

References:

1. Singer, M., *et al.* (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 315(8), 801-810.
2. Rudd, K. E., *et al.* (2020). Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet, 395, 100-111.
3. Vincent, J. L., *et al.* (2019). Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Critical Care, 23(1), 196.
4. Wentowski, C., *et al.* (2019). Sepsis in 2018. Anaesthesia & Intensive Care Medicine, 20(1), 6-13.
5. Diemeka, D. J., *et al.* (2019). Antimicrob Agents Chemother, 63(7), e00355-19.
6. https://www.cdc.gov/vitalsigns/pdf/2016-08-vitalsigns.pdf
7. Chakraborty, R. K., & Burns, B. (2023). Systemic Inflammatory Response Syndrome. [Updated 2023 May 29]. StatPearls.
8. Kilinc Toker, A., *et al.* (2021). Comparison of SOFA Score, SIRS, qSOFA, and qSOFA + L Criteria in the Diagnosis and Prognosis of Sepsis. Eurasian Journal of Medicine, 53(1), 40-47. doi: 10.5152.
9. Rhee, C., *et al.* (2020). Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Network Open, 3(4), e202899.
10. Evans, L., *et al.* (2021). Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Medicine, 47, 1181–1247.
11. Weiss, S. L., *et al.* (2020). Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Medicine, 46(Suppl 1), 10-67.
12. JAMA Network Open - Open Access Medical Research and Commentary
13. World Health Organization: www.who.int/news-room/fact-sheets/detail/sepsis consulted on 01/01/2024
14. Global Sepsis Alliance: www. https://globalsepsisalliance.org consulted on 01/01/2024

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