Definition and Epidemiology of sepsis

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Minimal abstract (171/200 words)

Here we review the epidemiology of sepsis, focusing on its definition, incidence and mortality, as well as the demographic insights and risk factors that influence its occurrence and outcomes. We address how age, sex and racial/ethnic disparities impact upon incidence and mortality rates. Sepsis is more frequent and severe among the elderly, males and certain racial and ethnic groups. Poor socioeconomic status, geographic location and pre-existing comorbidities also elevate the risk of developing and dying from sepsis. Seasonal variations, with an increased incidence during winter months, is also apparent. We delve into the predictive value of disease severity scores such as SOFA. We also highlight issues relating to coding and administrative data that can generate erroneous and misleading information, and the need for greater consistency. The Sepsis-3 definitions, offering more precise clinical criteria, are a step in the right direction. This overview will, we hope, facilitate understanding of the multi-faceted epidemiological characteristics of sepsis, and current challenges.

The evolution of sepsis definitions

- Current Sepsis-3 definition

Sepsis is a complex syndrome that entails significant perturbations of the body's physiological, pathological and chemical functions in response to an infectious trigger. The understanding and characterization of sepsis have evolved over three thousand years culminating in the present 'Sepsis-3' version, which defines sepsis as "*life-threatening organ dysfunction caused by a dysregulated host response to infection*" (Figure 1).[1] Clinically, this is identified by a ≥2 point increase in the Sequential Organ Failure Assessment (SOFA) score[2,3] relative to the patient's baseline. 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*." This is characterized by persisting hyperlactataemia >2 mmol/L *plus* vasopressor therapy to maintain mean arterial pressure (MAP) ≥65 mmHg despite the patient having received adequate volume replacement. [1]

In this context, organ dysfunction and failure serve as critical indicators for patient management. These terms are frequently used to describe abnormalities in specific organ systems. Dysfunction is the more nuanced and preferred term as it represents a continuum from mild to severe effects on the organ system, while failure indicates a yes-no binary state with a distinct cut-off that does not exist in reality. In sepsis, the involvement of various organ systems varies between individuals in terms of severity, quantity, and organ(s) affected. The presence of two or more dysfunctions is termed 'multi-organ dysfunction' Various scores have been developed to characterize dysfunction and the degree thereof, such as SOFA (Table 1) and MODS. These can be utilized clinically but in practice, are more used for epidemiology and research purposes, including trial enrolment.[4] No score is, however, specific for sepsis.

	SOFA Score 0	SOFA Score 1	SOFA Score 2	SOFA Score 3	SOFA Score 4
Respiratory system: PaO_2/FiO_2 kPa (mmHg)	≥53.3 (400)	<53.3 (400)	<39.9 (300)	<26.7 (200) + respiratory support	<13.3 (100) + respiratory support
Coagulation system: Platelets x $10^3/\mu L$)	≥150	<150	<100	<50	<20
Hepatic system: bilirubin µmol/L (mg/dL)	<20 (1.2)	20-32 (1.2-1.9)	33-101 (2.0-5.9)	102-204 (6.0-11.9)	>204 (>12)
Cardiovascular system [a]	MAP >70 mmHg	MAP <70 mmHg	Dopamine <5 µg/kg/min, OR Dobutamine (any dose)	Dopamine 5-15 µg/kg/min OR Epinephrine ≤0.1 µg/kg/min OR Norepinephrine ≤0.1 µg/kg/min	Dopamine >15 µg/kg/min OR Epinephrine >0.1 µg/kg/min OR Norepinephrine >0.1 µg/kg/min
Central Nervous System: Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal System:					
• Creatinine µmol/L (mg/dL)	<110 (<1.2)	111-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9)	>440 (>5)
• Urine output mL/day				<500	<200

Table 1 SOFA Score: FiO_2 - fraction of inspired oxygen, MAP – mean arterial pressure; PaO_2 – partial pressure of oxygen; a: Catecholamines must be given for at least one hour.

- Why have definitions and criteria changed?

The 'Sepsis-3' criteria have shifted the focus from the identifying pathogen to stressing the importance of the host's dysregulated reaction to this trigger. If this reaction is intense enough, organ dysfunction ensues.

Previous versions of the sepsis definitions characterized “sepsis” as an infection in conjunction with ≥2 of the 4 systemic inflammatory response syndrome (SIRS) criteria (Table 2). This was first coined by Bone and colleagues in the first set of definitions (now called ‘Sepsis-1’) published in 1992.[5] The motive for this work was to aid identification of suitable patients for entry into early randomized controlled trials in sepsis.[6] However, SIRS is non-specific and describes a host response common to any inflammatory condition that includes not only infection but also major surgery, trauma, pancreatitis, ischemia, autoimmune disorders, burns, adverse drug reactions and so forth. “Severe sepsis” was identified when sepsis was coupled with ambiguous and inadequately specified features such as ‘*organ dysfunction, poor blood flow, or low blood pressure*’. Septic shock was deemed to be present when severe sepsis was associated with ongoing hypotension despite adequate fluid replacement, along with non-specific signs of abnormal blood flow including ‘*elevated lactic acid levels, reduced urine output, or abrupt mental changes’*. The imprecise nature of these terms contributed to inconsistent criteria used in clinical trials and epidemiological studies. Depending on the criteria applied, the control group mortality rate in 65 studies of “septic shock” ranged from 13.8-84.6%.[7]

Table 2: Systemic inflammatory response syndrome (SIRS) criteria

tachycardia (heart rate >90 beats/min),
tachypnoea (respiratory rate >20 breaths/min)
fever or hypothermia (temperature >38 or <36°C)
leukocytosis (WBC >1200/mm^3), leukopenia (<4,000/mm^3) or bandaemia (≥10%)

The second iteration of the sepsis definitions ('Sepsis-2') published in 2003[6] acknowledged the lack of evidence to support any change to the definitions, and only offered a marked expansion of the list of signs and symptoms of possible sepsis. While an increasing number of SIRS criteria correlates with disease severity and mortality risk,[6] the application of SIRS is problematic for various reasons. Firstly, inflammation is a necessary protective host reaction to an insult and does not necessarily signify a pathological condition. Most mild infectious or non-infectious inflammatory conditions can fulfill SIRS criteria without leading to organ dysfunction or death. Conversely, one in eight patients admitted to Australasian intensive care units with presumed sepsis-related organ dysfunction did not meet the minimum SIRS criteria.[8] As both discriminant and concurrent validity are flawed, SIRS was removed from the latest Sepsis-3 definition. To simplify definitions, 'severe sepsis' has been replaced with 'sepsis' thus there is a progression from uncomplicated infection through sepsis (infection with organ dysfunction) to septic shock (sepsis plus fluid-unresponsive hypotension and hyperlactataemia.[1]

Sepsis-3 does not represent the final answer but it updates the concept of sepsis, taking into account our contemporary understanding of the syndrome, and offering standardized clinical criteria that can be readily and promptly collected in most hospital settings. This latter point

is crucial as global epidemiology and valid comparisons cannot be determined with tests that are not generally available. Critics have argued that the new criteria fail to promote precise medicine approaches based on individual patient genomic and cellular,[9] yet there is still no consensus as to what should be measured, notwithstanding cost and availability issues.

The new criteria should hopefully establish a solid foundation for improved comparisons between medical facilities, countries, and over time. Both prospective studies and retrospective ICU database analyses from many countries in Europe, Asia and South America have demonstrated an approximate 25-30% mortality rate from sepsis and 40-55% mortality rate from septic shock, in line with the original Sepsis-3 database findings. [10–12] There are, however, some notable exceptions with far worse outcomes[13,14] with the authors themselves acknowledging a higher-than-predicted mortality rate.

Sepsis-3 can also be utilized for research purposes and, potentially, enriching study populations. This has been evidenced by post-hoc analyses of the HYPER2S trial[15] and the VASST trial[16] showing markedly differing treatment-related outcomes depending on disease severity.

Sepsis epidemiology

Before discussing epidemiological data (Figure 2) in more detail, it is worth highlighting that many studies are estimates often based on assumptions and extrapolations that may not necessarily be accurate.

• Diagnostic uncertainty

The variable and often indistinct nature of sepsis has created significant challenges for both patient diagnosis and epidemiological studies. No specific test exists other than microbiological identification of an infectious pathogen. Unfortunately, a likely pathogen is only identified in 30-50% of cases; even then, questions often arise as to whether the organism is pathogenic or not, for example coagulase-negative *Staphylococci*. A further challenge is time to identification of the pathogen. Up to 40% of sepsis cases (especially of chest origin) are subsequently traced back to non-bacterial causes.[17]

In the absence of a positive pathogen identification, there is a large and necessary dependency upon clinical suspicion, yet with differing levels of confidence. Not infrequently, unequivocal evidence of underlying infection is lacking and clinical and laboratory indicators are non-specific. Klein Klouwenberg et al[18] examined diagnostic accuracy in 2579 patients admitted to two Dutch ICUs with a presumptive diagnosis of sepsis. Subsequent adjudication determined 13% had a post-hoc infection likelihood of “none”, 30% “possible”, 25% probable and 33% definite. Others have reported similar uncertainty, e.g. Shappell et all.[19]

Sepsis-3 does preserve the overarching syndromic concept and does not attempt to differentiate between infection types, sites or patient categories. Therefore the same term can encompass a healthy young adult with urosepsis to an elderly person with peritonitis or

a middle-aged chemotherapy patient with hospital-acquired pneumonia. Mortality risks will vary accordingly. Sepsis-3 provides a broader, population-based tool to enhance coding and epidemiology.

Significant efforts are being expended at present on developing endotypes/subphenotypes to describe septic patients with differing biological signatures that carry different prognoses and likely different responses to host response-modifying therapies. Such signatures can be clinical,[20] transcriptomic,[21–23] proteomic or metabolomic.[24] However, no consensus exists at present and these have not been tested prospectively.

• (Mis)coding

Epidemiological studies in sepsis place a large reliance on administrative databases (electronic healthcare records, discharge coding, insurance claims data, death certificates) and an implicit assumption that these are accurate. However, when patient records are directly examined, these data often come up wanting, as evidenced by studies from the UK, United States, Sweden, Hong Kong and Australia.[25–28] For example, Rhee et al interrogated a database of more than 7 million patients collected between 2009-2014; using the Sepsis-3 criteria sepsis incidence was stable over this period whereas insurance claims-based sepsis incidence increased by more than 10% per year. [28] The same group found sepsis incidence was falsely elevated when using implicit sepsis codes while stable incidences were found with clinical definitions based on electronic health records.[29] Similarly, using a large US population database based on administrative claims data, sepsis-related mortality estimates were 15-140% higher than death certificate data.[30]

- The influence of diagnostic criteria on sepsis prevalence and incidence rates

Different definitions of sepsis can affect reported sepsis incidence and outcomes. Gaieski et al analyzed the annual incidence of severe sepsis and mortality between 2004-2009 from a large population database using four different methods of data abstraction.[31] They found a 3.5-fold variability in sepsis incidence ranging from 300-1031 per 100000 population and a mortality rate ranging from 15-30%.

When assessing the mortality of septic shock, different definitions of septic shock also alter epidemiological findings. Driessen *et al* analyzed mortality of affected patients according to Sepsis-2 vs. Sepsis-3 definitions. They reported a higher mortality in patients classified according to Sepsis-3 classification compared to patients meeting Sepsis-2 definition (38.9 vs. 34.0%).[32] In a large database including more than 600'000 admissions to 189 ICUs in the United Kingdom, sepsis incidence was similar between Sepsis-2 and Sepsis-3 criteria.[10] However, the population with septic shock was smaller when Sepsis-3 criteria were applied, suggesting better predictive validity of the new criteria.[10]

- Global incidence, prevalence and mortality

The Global Burden of Disease study by Rudd *et al*[33] claimed a global sepsis incidence of 48.9 million cases (95% uncertainty interval 38·9–62·9) and 11·0 million (10·1–12·0) sepsis-related fatalities in 2017, but with a falling incidence (37·0% (95% uncertainty interval [11·8–54·5]) and mortality (52·8% [47·7–57·5]) since 1990. Around 40% of cases occurred in children under 5 years old.[33] It should be stressed that these numbers are crude estimates that are potentially highly inaccurate; extrapolation of death rates was made from just four countries

from death certificate data and from only ten countries for determining the incidence. Indeed, their findings were contradicted in part by a meta-analysis including searches from 13 electronic databases. This suggested a pooled incidence of 189 [95% CI 133, 267] hospital-treated sepsis cases per 100,000 person-years, with an estimated mortality rate of 26.7% [22.9, 30.7]. For ICU-treated sepsis they estimated the incidence as 58 [42, 81] per 100,000 person-years, with a hospital mortality rate of 41.9% [95% CI 36.2, 47.7]. However, they argued that sepsis incidence was *increasing*, with a 46% rise in declared hospital cases observed after 2008.[34]

Markwart *et al* reviewed 51 studies of which 22 were from low- and middle-income countries, 28 were in adult ICUs, 13 neonatal ICUs and 10 hospital-wide.[35] They estimated that the pooled incidence of hospital- and ICU-acquired sepsis was around 9 per 1000 patients and 57 per 1000 patients, respectively. A recent population-level database analysis from Eastern Denmark (2.6 million inhabitants) using Sepsis-3 criteria identified 451,825 emergency department encounters of which suspected infection was registered in 60,316, sepsis was present in 28,472, and 8027 were defined as having septic shock.[36] National data from England in 2017-18 (population 55.6 million) identified 1.73 million emergency hospital admissions with a discharge code indicating either bacterial infection or sepsis as the reason for admission.[37] Contemporaneous UK critical care admissions with an ICU discharge diagnosis of sepsis numbered 44,115 (including admissions for hospital-acquired sepsis), of whom 13,455 died.

The large multinational EPIC 24-hour point prevalence study conducted at 1150 centers in 88 countries in 2017 indicated 54% of 15202 ICU patients were being treated for suspected or proven infection, of whom 1760 (22%) were ICU-acquired.[38] Overall hospital mortality was

30%. The point prevalence however varied from 43% in Australasia to 60% in Asia and the Middle East.

Mortality rates also vary across the available literature. Again, inconsistent coding is likely to play a large part underlying this variation. A systematic review of 170 studies published between 2009-19 identified a 90-day sepsis mortality of 32.2% (95% CI 27.0–37.5%) and 90-day septic shock mortality of 38.5% (95% CI 35.4–41.5%).[39] As described above, definitions used for septic shock were highly variable before the Sepsis-3 definitions were introduced in 2016 so the updated mortality risk from septic shock is likely much higher.[40]

- Geographical differences and influences

Developed countries have a different spectrum of septic illnesses to less developed countries. The Global Burden of Disease study[33] identified lower respiratory tract infections as the commonest cause of infection-related death worldwide followed by diarrhoeal diseases, HIV/AIDS, malaria, tuberculosis, meningitis and typhoid and paratyphoid. In a meta-analysis of 15 studies reporting outcomes of sepsis in sub-Saharan Africa, two-thirds of the 2800 patients included were HIV-infected.[41] In-hospital mortality for sepsis and severe sepsis (using Sepsis-2 criteria) was 19% and 39%, respectively; HIV positivity was associated with a higher mortality risk.

Mortality rates are generally similar in developed countries[39] and lower than in less affluent countries, albeit fewer data are available from such locations.[33] Various factors are implicated including social deprivation and access to healthcare. The socio-demographic index (SDI) is a composite ranking measure including income, education and fertility rates .[33] The highest age-standardized case fatality from sepsis was observed in countries with a low SDI.[33] The same inverse relationship was seen for sepsis incidence, although not as strong.

A point prevalence study conducted in 386 adult ICUs in 22 Asian countries[42] reported 22.4% of patients were being treated for suspected/proven sepsis. Those being treated in poorer countries were younger with a lower severity of illness. Overall hospital mortality was 32.6% and significantly higher in low/low-middle income countries (adjusted odds ratio, 1.84; 95% CI 1.00–3.37; $P = 0.049$). A study from Brazil reported a higher mortality rate in patients treated in public (55.5%) compared to private hospitals (37.0%).[43] Low availability of resources and treatment adequacy were independently associated with worse outcomes.[44]

Demographic Insights

- Age, sex, race, social deprivation

Men are more likely to develop sepsis with some reports indicating a higher risk of dying compared to females.[33,45–47]

With respect to age, there is a biphasic distribution in terms of incidence with the majority of hospital admissions in children under 4 years of age or in a geriatric population.[33,37] Most deaths occur in older patients.[48,49] English data show 77.5% of sepsis-related deaths occur in patients over 75 years with only 150 deaths per year occurring in children between 0-18 years of age.[37] However, in low/low-middle income countries, sepsis mortality is reported to be highest in newborns.[33]

Sepsis mortality (adjusted for patient characteristics) was higher in black and Hispanic patients compared to white patients.[50] After adjustment for clinical presentation characteristics, strain on hospital capacity, initial ICU admission and inpatient deaths, black patients with sepsis and acute respiratory failure had a longer hospital length of stay, reasons for which are unclear.[51] Black patients with suspected pneumonia were less likely to receive

antibiotics within the first hours though this is likely related to differences in case mix and intensity of care provide by hospitals with higher proportions of black patients.[52] However, within the same hospitals, quality of care was similar for black and white patients.

Sepsis incidence was higher in less educated people and in whose travel distance to a pharmacy was increased.[53] People living in the American "Sepsis-Belt" of south-eastern states were significantly more likely to develop sepsis.[54] The population in this belt had lower average incomes and inferior education compared to other US regions. Similarly, household income and percentage of poverty in communities were associated with sepsis-related mortality.[55]

- Comorbidities and other risk factors

Mortality also differs by infection site; comparable mortality rates were seen for abdominal or pulmonary origin (~19%) compared to 13% for renal sepsis.[56] Chronic obstructive pulmonary disease, cardiovascular diseases, diabetes mellitus, malignancies, pre-existing liver/kidney diseases and substance abuse are also associated with a higher risk of contracting sepsis that requires ICU admission.[57]Risk is also increased if more than one comorbidity is present.[10] A meta-analysis found mortality rates were higher in patients with HIV compared to non-HIV patients, especially in low income countries.[58]

Disease severity also influences the burden of sepsis and outcomes. A greater degree of organ dysfunction, commonly assessed by the Sequential Organ Failure Assessment (SOFA) score, was associated with a progressive increase in mortality risk.[1,2] Of note, vague, nonspecific symptoms and signs at hospital presentation were associated with a higher risk of mortality in patients with septic shock.[59] This was particularly apparent in elderly, frail patients and may be related to prolonged delays in antibiotic administration or, possibly, ceilings of care.

Finally, genetic factors may also confer different risks associated with either predisposition to sepsis or outcome. [60] No clear signal has been consistently identified in terms of risk associated with specific single nucleotide polymorphisms giving rise to different alleles. This may relate to racial differences[61] and/or epigenetic modifications that are still poorly characterized. [62–64]

- Seasonal variations

Some research has addressed seasonal variations in sepsis incidence. A large population database study showed a 17.7% increase between autumn and winter in sepsis incidence, mainly related to a 40% rise in respiratory infections.[65] Although disease severity was comparable, mortality was 13% higher in winter compared to summer. Hypothermia as a presentation of sepsis was also more common in winter.[66]

Current trends and future directions in sepsis epidemiology

- Artificial intelligence

A recent study using AI tested a diagnostic algorithm and found high predictive accuracy more than 10 hours before disease onset.[67] Compared to human prediction, the AI algorithm could reduce false positive detections by up to 17%.[67]

- Implications for health policy and planning

A recent international expert statement published by the WHO summarized future priorities and directions in epidemiological research related to sepsis.[68] It proposed funding for generation of new epidemiological evidence, achievement of international consensus relating to sepsis case definitions, promotion of surveillance research, infection prevention and hygiene measures and the development of recommendations for reporting related to epidemiological studies. Over the longer term, this panel recommended strengthening evidence on the role of sepsis in high-risk populations (e.g. vulnerable patients, elderly), to find more evidence on causative microorganisms and their antimicrobial susceptibility profiles, and to develop diagnostic and prognostic assays (e.g. with biomarkers) to promote early recognition. Specifically for low-resource settings, advocacy, assistance, funding of population-based primary research, strengthening of laboratory capacity, and promotion of the linking of research results to therapeutic approaches that might reduce disease burden were highlighted.

Conclusion

In conclusion, the Sepsis-3 definition and associated clinical criteria currently stands as the most up-to-date and comprehensive framework for identifying this complex syndrome, albeit acknowledging the frequent difficulty in formally diagnosing an infectious trigger. The epidemiology of sepsis remains intricate, shaped by various factors such as demographics, comorbidities, and seasonality. Older adults are particularly vulnerable. Disparities in sepsis outcomes exist among racial and ethnic groups, socio-economic factors and geographic location. Comorbidities such as COPD and cardiovascular diseases significantly elevate risks while disease severity, often assessed by the SOFA score, serves as a robust predictor of outcomes. Seasonal trends show an increased incidence of sepsis during winter. A nuanced understanding of these epidemiological factors is crucial for both clinicians and policy-makers, aiding more precise diagnostic strategies and targeted healthcare interventions. Future research should focus on elucidating the mechanisms behind these disparities and evaluating the effectiveness of interventions.

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