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Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes

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Abstract

Sepsis has been around since the dawn of time, having been described for more than 2000 years, although clinical definitions are recent. The consensus sepsis definitions have permitted worldwide epidemiological studies of sepsis to be conducted. We now recognize the common nature of sepsis and the consistency of its disease – particularly severe sepsis and septic shock. The incidence of sepsis, severe sepsis and septic shock continues to increase, and although Gram-positive bacterial pathogens remain the most common cause of sepsis, fungal organisms are increasing rapidly. We have made progress over the past half-century in identifying and treating patients with sepsis, and decreasing fatality rates reflect this progress. However, owing to the increasing incidence of sepsis, the number of people who die each year continues to increase. The mortality with sepsis, particularly related to treating organ dysfunction, remains a priority to clinicians worldwide and is deserving of greater public health attention.

Keywords

critical illness; infection; intensive care unit; sepsis

The purpose of this review is to discuss the current understanding of sepsis epidemiology, with particular attention to changes in incidence and changes in pathogenic organisms over time. This article will start by discussing the initial and the current clinical definitions of sepsis, including recent considerations for revision, and use that definition to explore the general epidemiology of sepsis in both the developed and the developing world. The final section will discuss temporal changes in clinical outcomes for patients with sepsis.

Sepsis definitions

Sepsis historically has been a condition that is difficult to identify and diagnose. As far back as 100 BC, Marcus Terentius Varro, the ancient Roman scholar and writer (116 BC–27 BC), was quoted as noting that “small creatures, invisible to the eye, fill the atmosphere, and breathed through the nose cause dangerous diseases.” Perhaps the most prescient description of sepsis was by the historian, philosopher, humanist and Renaissance author Niccolo Machiavelli (1469–1527), as reported in his treatise, *The Prince*, in 1513. Early in the book, he very eloquently stated that, `hectic fever, at its inception, is difficult to recognize but easy

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to treat; left unattended it becomes easy to recognize and difficult to treat.' Although hectic fever is not the name by which we know sepsis now, the description of a disease that is difficult to recognize in its early stages, at a time when the condition may be amenable to treatment, and more difficult to treat in its later more obvious stages is a clear description of the more severe forms of sepsis.

In an attempt to better clinically understand sepsis, in the past century, a variety of definitions have been developed. Among the earliest concepts was to consider sepsis as a systemic host response to an infection [1]. In fact, it was classically described by the eminent American physician William Osler (1849–1919) in his seminal observation that the patient appears to die from the body's response to an infection rather than from the infection itself. Closer to the modern era, in 1972 this concept was reinforced in a medical review, noting that “it is our response that makes the disease” [2]. The general concept has long been considered a form of poisoning, often considered as blood poisoning, but more practically representing the presence of pathogenic organisms or their toxins in the blood or tissues.

It was the failure of these medical definitions, [3] and myriad attempts at developing diagnostic tools and assays to identify sepsis [4], that led to a consensus conference focusing on a way to clinically define sepsis. In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) jointly published the consensus definitions of sepsis (see Table 1) [5]. These are among the most frequently cited definitions in critical care and they have become second nature to many critical care physicians (intensivists) and other intensive care providers throughout the world. Their novel description of the systemic inflammatory response syndrome criteria and specific definitions for sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome were all critical developments in the field of sepsis (see Figure 1). Since these consensus definitions had limitations in clinical use, they were revisited in 2001 [6]. Although there were many limitations recognized of the current definitions, there was no superior alternative identified. There was significant consideration to expanding the foundational `systemic inflammatory response syndrome' criteria to include other parameters that may be associated with sepsis. However, these represented a broadening of the potential diagnostic criteria that would, if anything, make the sepsis definition less specific than it was previously. In addition, some of the criteria overlapped with the definitions developed for identifying organ dysfunction, which is a critical component of distinguishing severe sepsis and septic shock. Perhaps the most important result from the 2001 Consensus Conference was the proposal for a `Predisposition, Infection, Response and Organ dysfunction' (PIRO) system for staging sepsis. The concept of PIRO was analogous to staging cancer or other medical conditions, and it appears that these criteria do allow for differentiating groups of patients with sepsis [7].

Longitudinal changes in incidence

The clinical consensus definition of sepsis has allowed for a number of studies of epidemiology to be conducted. At present, there have been studies in most developed and in many developing countries using this clinical definition. In general, sepsis occurs in approximately 2% of all hospitalizations in developed countries. Sepsis may occur in between 6 and 30% of all intensive care unit (ICU) patients, with substantial variation due to the heterogeneity between ICUs [8]. For example, sepsis may occur in a very high proportion of medical or trauma ICU patients in a large urban hospital but may comprise a relatively small proportion of ICU patients in a community cardiac or surgical ICU. In general, more than 50% of severe sepsis patients will require intensive care services.

There has been less attention on the incidence of sepsis than there is on the incidence of severe sepsis and septic shock. This is perhaps appropriate given that sepsis may be present in nearly all patients requiring hospitalization with an infection, while severe sepsis is present in between half and three-quarters of critically ill patients [9]. Furthermore, it is the patients with organ dysfunction and high severity of acute illness that consume much of the resources and are at high risk for complications and death. In most developed countries, the incidence of severe sepsis has been identified as between 50 and 100 cases per 100,000 people in the population [10]. In general, the incidence of sepsis is three to four-times higher, reflecting the relative percentage of patients who develop organ dysfunction and thus meet more severe definitions (severe sepsis or septic shock) [11]. In the past decade we have realized that there have been significant longitudinal changes in the incidence of sepsis, most obviously in the USA. A two-decade study of US hospitalizations identified an increase in the incidence of sepsis among hospitalized patients by 8.7% per year [11]. At present, it is estimated that there are more than 1,000,000 cases of sepsis among hospitalized patients each year in the USA. Numerous reports have shown the incidence of sepsis and severe sepsis increasing in excess of the growth of the population [11–14]. Similar reports exist from the UK, Australia and from Croatia [15–17].

The incidences of sepsis, severe sepsis and septic shock are less well-described in the developing world [18]. There are more data available on the incidence of infectious diseases, which remains a constant battle for which there are many high incidence conditions. As infectious diseases are inevitably the cause of sepsis, sepsis presumably is of similar or even greater importance in these areas of the world than in the most developed nations. Sepsis is more frequent in younger individuals in the developing world and the responsible organisms are more likely to be Gram-negative enteric pathogens and atypical pathogens such as malaria [19]. It should also be noted that patients dying of infectious diseases inevitably die of sepsis and sepsis-related organ dysfunction. As stated earlier, it is not the infection that kills people but rather it is the host immune response attempting to fight the infection that ultimately may cause the fatal outcome. With that in mind, it is apparent that we inevitably underestimate the incidence of the more severe forms of sepsis in areas where more attention is given to infectious diseases and to their causes and complications.

The incidence of sepsis is affected by a variety of patient-specific factors. We have long recognized that age is an important component of someone's risk for developing sepsis, as are a variety of comorbid medical conditions. Perhaps most obvious are conditions like HIV, cancer and diabetes, each of which may alter the immune system [20]. These conditions result in a significantly elevated risk for developing sepsis, and may also increase the risk of nosocomial sepsis given these individuals' frequent interactions with healthcare systems. More recently it has been recognized that race, ethnicity and gender may also contribute to the differential risk for developing sepsis [11,21,22]. In general, males have a higher risk for developing sepsis than females, regardless of age [11,14,21]. The mechanisms behind differential incidence based on race and ethnicity are less clear, but in general non-Caucasian races are at higher risk for developing sepsis compared with Caucasians [11,21–23].

Evolution of pathogens

The causative organisms for sepsis have evolved over many years. Originally sepsis was described, and strongly considered to be, a disease specifically related to Gram-negative bacteria [24]. This is because sepsis was considered to be a response to endotoxin – a molecule that was thought to be relatively specific for Gram-negative bacteria. In fact, some of the original studies of sepsis bore out that Gram-negative bacteria were among the most common causes of sepsis [25]. This resulted in a number of trials that focused on Gram-

negative therapies, and even highly specific therapies for endotoxin, which were felt to be potentially useful treatments for sepsis. We now recognize that sepsis may occur from any bacteria, as well as from fungal and viral organisms. More recent epidemiology studies reveal that Gram-positive bacteria have become the most common cause of sepsis in the past 25 years [11]. Large epidemiologic studies show Gram-positive organisms superceding Gram-negatives in the early- to mid-1980s as the most common cause of sepsis in the USA. According to the most recent estimates in sepsis, there are approximately 200,000 cases of Gram-positive sepsis each year, compared with approximately 150,000 cases of Gram-negative sepsis [11].

While bacterial causes of sepsis have increased with the general increases in incidence, fungal causes of sepsis have grown at an even more rapid pace [11]. This may represent a general increase in nosocomial cases of sepsis, or it may reflect our effective treatment of bacterial infections, thus promoting fungal infections to a more leading role. While there has been an overall increase in the number of fungal nosocomial infections, we have also observed shifts away from the most common *Candida albicans* organism to the more recalcitrant *torulopsis, glabrata* and *krusei* subspecies [26,27].

Sepsis tends to occur from specific and consistent sources. Respiratory infections are invariably the most common cause of sepsis, severe sepsis and septic shock [11,21,28]. Overall, respiratory infections account for approximately half of all cases of sepsis. The next most common causes are genitourinary and abdominal sources of infection with primary bacteremia and unknown sources being the next most common causes. The occurrence of acute organ dysfunction (i.e., severe sepsis) is related to the source of infection, as in patients with respiratory infections who are at higher risk for developing respiratory organ dysfunction.

Regardless of the era and the organisms, the treatment of infection is the cornerstone of antisepsis therapy. There are two particular components of antimicrobial therapy that are important. The first is early antimicrobial therapy, with initiation of antibiotics in an appropriate time interval depending on the location of the patient. There are particular data from patients with pneumonia, and from those with septic shock, that show that delays in antimicrobial therapy lead to a significantly increased risk of dying [29,30]. Especially critical for septic shock, the risk of dying increases by approximately 10% for every hour of delay in receiving antibiotics [30]. The other important component of antimicrobial therapy is appropriateness of the antimicrobial regimen. It may be intuitive that coverage of the appropriate organisms is critical, as failure to cover the appropriate organisms is synonymous with delays of antimicrobial therapy. A variety of studies of infected and septic patients show that inappropriate antimicrobial therapy is a consistent predictor of poor outcomes [31,32]. From a clinical perspective this means that the antimicrobial therapy must almost always be empiric. The choice of antibiotics, and the timing of their administration, cannot wait for isolation and identification of the causative organism and determination of the organism's sensitivity to various antibiotics. These principles underlie the observation that combination antimicrobial therapy may be superior to monotherapy [33]. In addition, in certain circumstances antibiotic therapy alone is not sufficient to treat the infection causing sepsis, in which case source control is also necessary to eradicate the infection [34,35].

Clinical outcomes

Patients with sepsis are classically considered to be patients who have a high risk of morbid complications and death. This is in large part owing to the organ dysfunction caused by sepsis, and the attendant complications of treating the organ dysfunction. Septic patients tend to be high resource consumers in the hospital and in the ICUs, and their presence

affects the outcomes of those ICUs overall. For example, ICUs with a higher percentage of patients with sepsis also inevitably have higher average mortality rates [8]. In addition, the costs of sepsis are quite substantial. There are estimates from around the world that consistently report cases of sepsis to cost from US$25,000 to $50,000 per episode [36–40].

There are many different ways to predict the risk of dying for patients with sepsis. The most facile approach may be to accurately classify the patient according to their stage of sepsis. Applying the consensus conference definition, rough estimates of fatality rates (the percentage of patients who die) are as follows:

- Sepsis: 10–20%
- Severe sepsis: 20–50%
- Septic shock: 40–80%

The PIRO system is attractive for its potential ability to group sepsis patients according to specific factors that may produce more homogeneous groups, such as comorbidities, type or source of infection and dysfunctional organ systems, among others. To date, whether PIRO staging is additive to this simple prediction schema remains to be determined.

Perhaps more important than these crude mortality estimates is that the risk of dying with sepsis has been falling over the past three decades. From data extending back to 1979, the risk of dying with sepsis was near 30% in the early years, and since the year 2000 the risk has been under 20% [11]. Similar results have also been observed when analyzing temporal changes in mortality from clinical trials of sepsis therapies [41]. Unfortunately, despite an apparent reduction in patients' risk of dying, owing to the increasing risk of dying, owing to the increasing incidence of sepsis, the total number of people dying with the condition each year continues to rise. In fact, the number of people dying from sepsis each year (estimated to exceed 200,000) is similar to the number of people dying with acute myocardial infarction, and far exceeds those who die from HIV, breast cancer or stroke. In the USA, sepsis is the tenth leading cause of death overall.

Expert commentary

Our understanding of sepsis has advanced exponentially over the past three decades, and has been enhanced by a clinically useful definition. The American College of Chest Physicians/Society of Critical Care Medicine consensus definition has been used for conducting studies of epidemiology as well as carrying out randomized clinical trials. Sepsis is among the most frequent conditions we encounter in ICUs, with the more severely ill patients being high resource consumers and at high risk for death. The incidence of sepsis, severe sepsis and septic shock continues to increase, with Gram-positive bacterial pathogens and respiratory infections being the most common causes of sepsis. Despite our improved understanding, which has reduced the risk of dying with sepsis, the number of people who die each year continues to increase due to an overall increase in the number of cases. Although efforts to improve public health by preventing and treating sepsis have been effective, such as the Surviving Sepsis Campaign, greater attention is still required to achieve the outcomes our sickest patients deserve.

Five-year view

The rapidity of advances in knowledge and epidemiology over the past 20 years portends even greater advances in clinical care. These advances will inevitably cause changes in the causes of sepsis, both in terms of organisms and sources. Although these changes may not be apparent on a 5-year time horizon, and these changes will create new challenges for both clinicians and researchers, it can be expected that sepsis-specific mortality will decline in the

next 20 years. As we further our epidemiological understanding of sepsis, we will better encompass the myriad causes, particularly in the developing world, and thus further grasp the full impact of sepsis for people around the world.

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Key issues

- The incidence of sepsis is increasing in all areas of the world where epidemiology studies have been conducted.
- Gram-positive bacteria have become the most common cause of sepsis, although fungal organisms are increasing most rapidly in incidence.
- Despite falling proportional fatality rates with sepsis, the total number of people dying with sepsis each year continues to increase due to the growing number of cases each year.

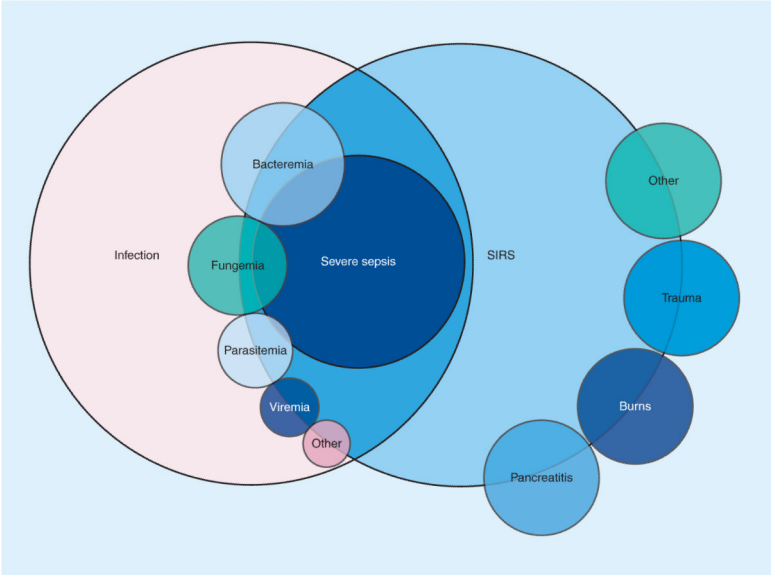

Figure 1. Relationship between systemic inflammatory response and infection, where the overlap indicates sepsis

SIRS: Systemic inflammatory response syndrome.

Table 1

Defining criteria of ACCP/SCCM named conditions.

ACCP/SCCM named condition	Defining criteria
SIRS	Core body temperature >38°C or <36°C HR ≥90 bpm Respirations ≥20/min (or $PaCO_2$ <32 mmHg) WBC ≥12,000/μl or ≤4000/μl or >10% immature forms
Sepsis	At least two SIRS criteria caused by known or suspected infection
Severe sepsis	Sepsis with acute organ dysfunction (including hypoperfusion and hypotension) caused by sepsis
Septic shock	Sepsis with persistent or refractory hypotension or tissue hypoperfusion despite adequate fluid resuscitation
MODS	The presence of organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention.

ACCP: American College of Chest Physicians; HR: Heart rate; MODS: Multiple organ dysfunction syndrome; $PaCO_2$: Partial pressure of carbon dioxide in the blood; SCCM: Society of Critical Care Medicine; SIRS: Systemic inflammatory response syndrome; WBC: White blood cell.