

Epidemiology of severe sepsis

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Severe sepsis is a leading cause of death in the United States and the most common cause of death among critically ill patients in non-coronary intensive care units (ICU). Respiratory tract infections, particularly pneumonia, are the most common site of infection, and associated with the highest mortality. The type of organism causing severe sepsis is an important determinant of outcome, and gram-positive organisms as a cause of sepsis have increased in frequency over time and are now more common than gram-negative infections.

Recent studies suggest that acute infections worsen pre-existing chronic diseases or result in new chronic diseases, leading to poor long-term outcomes in acute illness survivors. People of older age, male gender, black race, and preexisting chronic health conditions are particularly prone to develop severe sepsis; hence prevention strategies should be targeted at these vulnerable populations in future studies.

Sepsis and severe sepsis (sepsis accompanied by acute organ dysfunction) are leading causes of death in the United States and the most common cause of death among critically ill patients in non-coronary intensive care units (ICU).¹ Recent data suggest the annual cost of hospital care for patients with septicemia is \$14 billion in United States.² Therefore, sepsis and severe sepsis are important public health problems. This article focuses on the epidemiology of severe sepsis and discusses common etiologies, risk factors, and long-term outcomes. The information provided is focused primarily on developed countries, and the epidemiology of severe sepsis in resource-limited countries may differ substantially.

Definitions

In 1991, the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference proposed a broad framework to define systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis (Table 1).³ This syndrome was envisioned as a continuum of worsening inflammation, starting with SIRS, and evolving from sepsis to severe sepsis and septic shock. The criteria for SIRS were based on temperature, heart rate, respiratory rate, and white blood cell count. At least 2 of these 4 criteria had to be met to define SIRS. Although SIRS

often occurs in the setting of infection, noninfectious conditions, such as burns, acute pancreatitis, and trauma, can lead to SIRS. Sepsis was defined as the presence of the SIRS criteria and presumed or proven infection. Severe sepsis was defined as sepsis accompanied by acute organ dysfunction.

Although the 1991 Consensus Conference laid the framework to define sepsis, it had important limitations. The “2 out of 4” criteria for SIRS were arbitrary and not specific to sepsis alone. The criteria did not include biochemical markers, such as C-reactive protein, procalcitonin (PCT), or interleukin (IL)-6, which are often elevated in sepsis.

A 2001 Consensus Conference by the Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society was convened to modify these definitions.⁴ The criteria for sepsis were revised to include infection and presence of any of the diagnostic criteria shown in Table 2. These criteria were based on clinical and laboratory parameters. The conference participants acknowledged that there was no single parameter or a set of clinical or laboratory parameters that are adequately sensitive or specific to diagnose sepsis. Severe sepsis criteria remained unchanged and it was defined as sepsis with an organ dysfunction. Although there are several criteria to define organ dysfunction during sepsis, the use of the Sepsis-related Organ Failure (SOFA) score by Vincent and colleagues⁵ was recommended to define organ dysfunction during sepsis. A more explicit definition for septic shock was also proposed. Septic shock was defined as persistent hypotension with systolic blood pressure <90 mmHg or mean arterial blood pressure <70 mmHg, despite adequate fluid resuscitation.

Epidemiological studies of administrative data sets often rely on imprecise definitions such as ICD-9CM codes for “septicemia” and “bacteremia” along with separate codes for organ dysfunction,⁶ which may underreport the diagnosis of sepsis.⁷ Diagnosis of severe sepsis can be made more sensitive by combining codes for various infections (e.g., pneumonia) and acute organ system dysfunctions.¹

Epidemiology

Incidence and mortality

In the United States, the incidence of severe sepsis is estimated to be 300 cases per 100 000 population.¹ Approximately half of these cases occur outside the ICU. A fourth of patients who develop severe sepsis will die during their hospitalization. Septic shock is associated with the highest mortality, approaching 50%.

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Table 1. Criteria for SIRS, sepsis, severe sepsis, and septic shock based on the 1991 ACCP/SCCM Consensus Conference

Term	Criteria
SIRS*	2 out of the 4 following criteria:
	Temperature >38 °C or <36 °C
	Heart rate >90/min
	Hyperventilation evidenced by respiratory rate >20/min or arterial CO ₂ lower than 32 mmHg
	White blood cell count >12 000 cells/μL or lower than 4000 cells/μL
Sepsis	SIRS criteria with presumed or proven infection
Severe sepsis	Sepsis with organ dysfunction
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation

Note: *SIRS, systemic inflammatory response syndrome.

The cumulative burden of organ failure is the strongest predictor of death, both in terms of the number of organs failing and the degree of organ dysfunction.

In 2003, Martin and colleagues found an increase in septicemia incidence and septicemia-related deaths over the past 2 decades in United States.^{6,8} This trend is expected to continue due to aging of the population, increasing burden of chronic health conditions, and increased use of immunosuppressive therapy, transplantation, chemotherapy, and invasive procedures. National estimates of severe sepsis incidence are often based on use of administrative data sets. Changes in coding practices, particularly increased coding of organ dysfunction, may overestimate the rate of increase.⁹

Over the past 2 decades, the case-fatality has declined due to advances in supportive care for the critically ill.¹⁰ For example, since implementation of bundled care processes (e.g., Surviving Sepsis Campaign) and low tidal volume ventilation in patients with acute respiratory distress syndrome (ARDS), mortality among critically ill patients with severe sepsis has decreased over the past decade.¹¹⁻¹⁵

Point prevalence studies in the ICU are the simplest approach to describing the epidemiology of sepsis. For example, 32.8% of 895 patients in 254 Mexican ICUs had sepsis on a single day in 1995.¹⁶ Extrapolation of such data to population estimates assumes all patients with sepsis will be in an ICU. Even in the most advanced health care systems this is unlikely to be the case.¹ Prevalence studies have other limitations. For example, the prevalence may increase if illness duration increases with better survival, even if incidence falls. Data from point prevalence studies have been used to estimate population incidence,¹⁷ but without information on illness duration, these figures are difficult to interpret.

Prospective cohort studies in which incidence is directly observed are potentially more accurate. A cohort study of sufficient duration may also overcome problems of seasonal variation. However, cohort studies limited to ICU patients may underestimate the incidence. Extrapolating ICU incidence to population incidence remains flawed because not all patients with sepsis are

Table 2. Criteria for sepsis based on 2001 SCCM/ACCP/ATS/ESCM/SIS Consensus Conference

Term	Criteria
Sepsis	Documented (or suspected) infection with any one of the following clinical or laboratory criteria
General parameters	Fever, hypothermia, tachycardia, tachypnea, altered mental status, arterial hypotension, decreased urine output, significant peripheral edema, or positive fluid balance
Inflammatory parameters	Leukocytosis, leukopenia, hyperglycemia, increased C-reactive protein, procalcitonin, or creatinine, coagulation abnormalities, increased cardiac output, reduced mixed venous oxygen saturation
Hemodynamic parameters	Hypotension, elevated mixed venous oxygen saturation, elevated cardiac index
Organ dysfunction parameters	Arterial hypoxemia, acute oliguria, increase in creatinine level, elevated international normalized ratio or activated partial thromboplastin time, ileus, thrombocytopenia, hyperbilirubinemia
Tissue perfusion parameters	Hyperlactatemia, decreased capillary refill, or mottling

treated in an ICU. A discussion of the epidemiology of sepsis is therefore really one of “treated sepsis”.¹⁸ The threshold of eligibility for treatment almost certainly differs by time and country, with different cultural approaches to end-of-life care, different availability of acute hospital and ICU beds, varying levels of universal health insurance, and other cultural and economic factors.¹⁹ For example, in Spain in 2003 only 32% of patients with severe sepsis were admitted to the ICU²⁰ compared with 51.1% in the United States.¹ Furthermore, an unrepresentative sample of ICUs may bias the result. Most countries have only quantified the epidemiology of sepsis in their intensive care populations and the estimates would be influenced by the availability of ICU beds in each country. It has been postulated that the high ICU incidence of sepsis in countries such as the UK (27.1%) and Brazil (27.3%) reflects a scarcity of ICU beds, as only the sickest patients can be admitted.¹⁸ There are 8.6 ICU beds per 100 000 population in the UK compared with 38.4 and 30.5 per 100 000 in France and the United States,²¹ where the mean ICU frequency of sepsis is 12.4% and 12.6%, respectively.

Some of these problems are overcome using administrative databases that record data from an entire population or correctly weighted samples thereof. Such an approach relies on accurate coding of disease by personnel entering data for another purpose, usually reimbursement. Problems of case definition are particularly important when using administrative databases. For example, Gaieski et al. demonstrated an up to 3.5-fold difference in the incidence and mortality of severe sepsis depending on the method of database abstraction used.²²

Etiology and Site of Infection

Etiology

Gram-positive organisms as a cause of sepsis have increased in frequency over time and are now almost as common as

Table 3. Types of organisms in culture-positive infected patients and associated risk of hospital mortality (modified from reference 32)

	Frequency (%)	OR (95% CI)
Gram-positive	46.8	
<i>Staphylococcus aureus</i>	20.5	0.8 (0.6–1.1)
MRSA	10.2	1.3 (0.9–1.8)
<i>Enterococcus</i>	10.9	1.6 (1.1–2.3)
<i>S. epidermidis</i>	10.8	0.9 (0.7–1.1)
<i>S. pneumoniae</i>	4.1	0.8 (0.5–1.4)
Other	6.4	0.9 (0.7–1.2)
Gram-negative	62.2	
<i>Pseudomonas</i> species	19.9	1.4 (1.2–1.6)
<i>Escherichia coli</i>	16.0	0.9 (0.7–1.1)
<i>Klebsiella</i> species	12.7	1.0 (0.8–1.2)
<i>Acinetobacter</i> species	8.8	1.5 (1.2–2.0)
<i>Enterobacter</i>	7.0	1.2 (0.9–1.6)
Other	17.0	0.9 (0.7–1.3)
Anaerobes	4.5	0.9 (0.7–1.3)
Other bacteria	1.5	1.1 (0.6–2.0)
Fungi		
<i>Candida</i>	17.0	1.1 (0.9–1.3)
<i>Aspergillus</i>	1.4	1.7 (1.0–3.1)
Other	1.0	1.9 (1.0–3.8)
Parasites	0.7	1.3 (0.5–3.3)
Other organisms	3.9	0.9 (0.6–1.3)

OR, odds ratio; CI, confidence interval; MRSA, methicillin-resistant *S. aureus*

gram-negative infections,^{6,23-25} likely due to greater use of invasive procedures and the increasing proportion of hospital-acquired infection.²⁶ More frequent use of broad-spectrum antibiotics in increasingly sick patients who remain in the ICU for longer periods of time has likely resulted in an increased bacterial resistance over time.^{27,28} Antibiotic resistance is problematic, prolonging length of stay and duration of mechanical ventilation, although the effect on mortality is uncertain.²⁹⁻³¹ International variations in the implementation of the two main strategies to control resistance (the more rational use of antibiotics and the prevention of cross-infection between patients) may explain different rates in different countries.²⁸

The type of organism causing severe sepsis is an important determinant of outcome. Although most recent studies have suggested an increasing incidence of gram-positive organisms, the latest European Prevalence of Infection in Intensive Care (EPIC II) study reported more gram-negative organisms (62.2% vs. 46.8%).³² Patterns of infecting organisms were similar to those in previous studies, with predominant organisms being *Staphylococcus aureus* (20.5%), *Pseudomonas* species (19.9%), *Enterobacteriaceae* (mainly *E. coli*, 16.0%), and fungi (19%). *Acinetobacter* was involved in 9% of all infections, with significant variation of infection rates across different regions (3.7% in

Table 4. Common sites of infection in patients with severe sepsis by sex and associated crude mortality rates (based on Mayr et al.)³⁷

Site of infection	Frequency (%)		Mortality (%)	
	Male	Female	Male	Female
Respiratory	41.8	35.8	22.0	22.0
Bacteremia, site unspecified	21.0	20.0	33.5	34.9
Genitourinary	10.3	18.0	8.6	7.8
Abdominal	8.6	8.1	9.8	10.6
Device-related	1.2	1.0	9.5	9.5
Wound/soft tissue	9.0	7.5	9.4	11.7
Central nervous system	0.7	0.5	17.3	17.5
Endocarditis	0.9	0.5	23.8	28.1
Other/unspecified	6.7	8.6	7.6	6.5

North America vs. 19.2% in Asia). The only organisms associated with hospital mortality in multivariable logistic regression analysis were *Enterococcus*, *Pseudomonas*, and *Acinetobacter* species.³² The microbiologic results of the EPIC II are summarized in Table 3.

A large metaanalysis of 510 studies reported that gram-negative bacteremia was associated with a higher mortality compared with gram-positive bacteremia.³³ The most common bloodstream infections were due to coagulase-negative *Staphylococcus* and *E. coli*, but these were associated with a relatively low mortality (20% and 19%, respectively) compared with *Candida* (43%) and *Acinetobacter* (40%) species. Gram-positive pneumonia due to *Staphylococcus aureus* had a higher mortality (41%) than that due to the most common gram-positive (*Streptococcus pneumoniae*, 13%), but the gram-negative bacillus *Pseudomonas aeruginosa*, had the highest mortality of all (77%). This study demonstrated the interaction of organism and site of infection in determining mortality, and called for this to be incorporated into the risk stratification of clinical trials. However, approximately a third of patients with severe sepsis never have positive blood cultures.³⁴ Before ascribing causative risk to a particular organism, it is also necessary to take into account the confounding effect of the context in which the organism most commonly develops. For example, the association of *Acinetobacter* with high mortality probably reflects the tendency of *Acinetobacter* to develop as a nosocomial infection after a prolonged ICU course in patients with many comorbidities. These factors, rather than the organism's virulence, may explain the high associated mortality.

Site of infection

Respiratory tract infections, particularly pneumonia, are the most common site of infection, and associated with the highest mortality.³⁵ However, the relative importance of pneumonia has decreased over time.²⁶ Men and alcoholics are particularly prone to developing pneumonia,³⁶ while genitourinary infections are more common among women.^{1,35} Other common sources of infection include abdominal, skin, and soft tissue, device-related, central nervous system, and endocarditis.^{1,37} Common sites of infection in severe sepsis patients are summarized in Table 4.

Risk Factors

Risk factors for severe sepsis can broadly be divided into risk factors for infection and, contingent upon developing infection, risk factors for organ dysfunction. Most of the risk factors of severe sepsis described in this paragraph relate to the infection risk, as risk factors that predispose someone with an infection to developing acute organ dysfunction are less well understood.³⁷

For example, age, male gender, black race, and increased burden of chronic health conditions are important risk factors for severe sepsis. Moreover, a recent study reported an inverse relationship between socioeconomic status and the risk of blood stream infection.³⁸ The incidence of severe sepsis increases disproportionately in older adults, and more than half of severe sepsis cases occur in adults over 65 y of age.³⁷ More than half of patients who develop severe sepsis also have at least one chronic health condition. Severe sepsis is more likely to occur in individuals with chronic obstructive pulmonary disease, cancer, chronic renal and liver disease, and diabetes. Other risk factors include residence in long-term care facilities, malnutrition, and use of immunosuppressive medications and prosthetic devices. Finally, abnormalities in the immune response to infection, as described below, increase risk of infection and severe sepsis. These abnormalities may be secondary to chronic diseases or age (i.e., immunosenescence).

Despite improved understanding of clinical risk factors influencing susceptibility and outcomes of sepsis, why some subjects develop severe sepsis and succumb to the infection while others do not, remains unclear. Thus genetic factors have been examined to explain variability in susceptibility and outcomes of infection. A study by Sorensen and colleagues³⁹ suggests that genetic factors may be more important in outcomes of infectious diseases compared with cardiovascular disease. In this study, adopted children whose biological parents died due to infectious causes had a 5.8-fold increased risk of dying due to infections. In comparison, the increased risk of death due to cardiovascular causes was 4.5-fold if their biological parents died of cardiovascular causes. Because sepsis is common and often fatal, the pattern of inheritance is unlikely to be Mendelian, where phenotypic differences are attributed to a single gene. Multiple genes may interact with pathogens (environmental factors) and influence susceptibility, response and outcome of sepsis. Some of the candidate genes that have shown promising results in preliminary studies include tumor necrosis factor (TNF), plasminogen activator inhibitor (PAI)-1, Toll-like receptor (TLR)-1 and TLR-4, and the Mal functional variant required for downstream signaling of TLR-2 and TLR-4.⁴⁰⁻⁴² A single center study in Belgium reported an association of MASP2 and NOD2/TLR4 genotypes with susceptibility to bacteremia and in-hospital mortality, respectively.⁴³

The relative contribution of clinical and genetic factors to susceptibility and outcomes of severe sepsis remains unclear. Genetic factors may play an important role in younger individuals but could be less important in older adults where chronic diseases may play a more important role. Furthermore, common variants may have a smaller attributable risk, while certain rare variants may lead to a higher attributable risk. Recent advances

in technology using genome-wide scans, where up to 1 million polymorphisms can be assayed in a single individual will allow identification of novel genetic variants.

Environmental risk factors

Severe sepsis is more common in colder months, both in the UK (35% higher in winter than in summer)⁴⁴ and US (17.7% higher in fall than in summer).⁴⁵ The case fatality rate for sepsis is also higher in winter, despite similar severity of illness. Respiratory infections have the greatest seasonal change, with their highest incidence in colder months, whereas genitourinary infections are significantly more frequent in summer. This seasonal variation relates to climate and is reflected by the regional differences within the US: incidence variation is highest in the northeast and lowest in the south. Recent studies have also explored the relationship of light exposure and critical illness. Consistent with the winter immunoenhancement theory, a shorter exposure to sunlight (i.e., photoperiod) in the month before critical illness was associated with a reduced risk of death in a single center observational cohort study.⁴⁶ However, once patients were in the ICU their exposure to natural light was almost negligible and hence future studies are warranted whether manipulating light exposure, before or during ICU admission, can enhance survival.

Special Populations

As mentioned above, increased burden of chronic health conditions are important risk factors for severe sepsis. Many comorbidities such as diabetes and chronic renal failure influence susceptibility to and outcome from severe sepsis.³⁷ However, some patient populations deserve special mentioning.

Malignancy

Cancer is one of the most common co-morbidities among patients with severe sepsis.⁴⁷ Analysis of a subgroup of patients with cancer in the 1979–2001 National Hospital Discharge Survey found cancer of all types increased the risk of developing sepsis almost 10-fold. Malignancy increased the risk of sepsis more than any other comorbidity, and the source of infection was related to the type of cancer; for example lung cancer patients were particularly likely to develop pneumonia. Sepsis contributed to 30% of all hospitalized cancer deaths. Cancer increased the case fatality rate of sepsis by 55%. However this is declining with time (cancer associated sepsis case fatality rates fell from 44.7% in 1979 to 23.8% in 2001), perhaps due to safer chemotherapy, or maybe just in parallel to the overall improvement in sepsis treatment. While the risk of developing severe sepsis was 8.7 times higher in hematological malignancy compared with solid tumors, the in-hospital mortality from severe sepsis was similar in each group.

Obesity

Obesity is a fast growing epidemic worldwide and is associated with other morbid conditions including diabetes, cardiovascular and respiratory diseases as well as cancer.⁴⁸ The effects of obesity on severe sepsis susceptibility and outcomes are not well described, but there is accumulating evidence that obese patients are more susceptible to infections and more likely to develop

serious complications of common infections.⁴⁹ Recently, Arabi et al. reported similar outcomes for obese and normal weight patients with septic shock in an international multi-center study after adjusting for baseline characteristics and treatment interventions.⁵⁰ Interestingly, obese patients received less fluid resuscitation and lower doses of antimicrobial agents adjusted for body weight compared with normal weight patients. The intricacies of caring for morbidly obese critically ill patients have been nicely summarized by El-Solh.⁵¹

Human immunodeficiency virus (HIV)

The epidemiology of sepsis in patients with HIV is changing significantly with advancements in highly active antiretroviral therapy (HAART) and *Pneumocystis jirovecii* prophylaxis. Over the past decade, the proportion of HIV-positive patients admitted to the ICU has steadily increased, as has their overall survival.⁵² Compared with the pre-HAART era, most HIV-positive patients who are hospitalized or admitted to the intensive care unit die of non-AIDS-related illness, the most common being sepsis.⁵³⁻⁵⁵

Data from a recent single center study in the United States found approximately 13.7% HIV-positive patients among all ICU admissions, with an overall in-hospital mortality of 42%.⁵⁴ Among HIV-positive patients, 194 acute infections were identified, of which the majority were nosocomial or healthcare-associated (57.7%). The remainder were AIDS-related (28.4%) or community-acquired (13.9%). Similar to the “general” population, sepsis in AIDS patients is increasingly due to multi-resistant organisms.⁵⁶

Children

The subject of pediatric sepsis is discussed in detail in this special issue on sepsis (see contribution by Randolph and McMulloh).

Analysis of a large administrative database using hospital discharge data from 7 US states recently reported an 81% increase in pediatric sepsis cases between 1995 and 2005, corresponding with an increased prevalence from 0.56 to 0.89 per 1000 pediatric population.⁵⁷ This increase was largely driven by a disproportionate increase in severe sepsis in neonates, particularly those with very low birth weight (9.7 vs. 4.5 per 1000 births). Of cases where a site of infections was identified, respiratory (48.9%) and primary bacteremia (18.1%) were the two most common.

Out-of-hospital severe sepsis

The emphasis on early recognition and aggressive treatment of sepsis was illustrated by the “early goal directed therapy” study, which showed that early aggressive resuscitation measures significantly improved mortality.⁵⁸ As a consequence, early fluid resuscitation, vasopressor support and blood transfusion to improve hemodynamics have been incorporated into treatment recommendations. Nevertheless, a recent multicenter cohort study showed that out-of-hospital interventions including fluid resuscitation, monitoring, and serial vital signs occurred in less than half of subjects.⁵⁹ Hence, there is a need to address the role of out-of-hospital interventions in improving clinical outcomes in severe sepsis and recognition strategies for severe sepsis before hospital arrival, as the limited data available suggest that only a third of patients with severe sepsis who are transported to the hospital

with emergency medicine services (EMS) receive out-of-hospital fluid resuscitation.⁶⁰

Sex and race

Women appear to be at lower risk of developing sepsis than men.^{1,61} Whether the greater male risk of developing severe sepsis reflects an increased risk of developing infection or of progressing to severe sepsis is not known, as are the underlying mechanisms of these disparities. A combination of differences in chronic disease burden, particularly subclinical disease, social and environmental factors, and genetic predisposition causing differences in the host immune response to infection likely contribute to the observed differences. For example, healthy female volunteers showed a more pronounced pro-inflammatory response after endotoxin infusion compared with healthy men.⁶² In addition, men tend to be treated more aggressively and undergo more invasive procedures,⁶³ whereas women more frequently have a “do not resuscitate” order written.⁶⁴ Another paper in this special issue by Angele et al. explores the role of estrogens and androgens that may account for the gender differences in sepsis outcomes.

Epidemiological studies consistently report a higher incidence of severe sepsis among black compared to white patients.^{65,66} The higher severe sepsis rate is due to both a higher infection rate in black patients and a higher risk of developing acute organ dysfunction.³⁷ These results are independent of sex, robust across different sources and etiologies of infections, and persist after adjusting for poverty level and hospital effect. The underlying mechanisms of racial disparities in infection and severe sepsis are poorly understood. Similar to gender differences, a combination of differences in chronic disease burden, social and environmental factors, and the immune response to infection likely contribute to the observed differences in infection and severe sepsis-related hospitalization rates. A higher prevalence of chronic kidney disease and diabetes among black patients hospitalized for infection may partly explain higher infection-related hospitalization rates among black patients. Furthermore, the differences in co-morbidities did not explain higher risk of organ dysfunction among those hospitalized for infection. Differences in host immune response may partly explain these differences,^{67,68} and recent studies suggesting polymorphisms in key proteins involved in the host response to infection suggest an increased susceptibility to severe infections and septic shock among people of African descent.^{41,42} In addition, the majority of black patients receive care for common infections, such as community-acquired pneumonia, at hospitals that provide overall poorer quality of care regardless of race. Thus, policy interventions directed at hospitals that provide care to large number of black patients seem most promising to reduce racial disparities for CAP and severe sepsis.⁶⁹

Long-Term Outcomes

The traditional focus of care in patients with infectious disease has been to reduce short-term mortality and clinical trials have used 28-d or 90-d mortality as an endpoint. However, recent studies suggest that infection may worsen long-term outcomes.⁷⁰⁻⁷³ While it is commonly perceived that serious infections occur in

older subjects with chronic health conditions and that these conditions contribute to higher mortality even after recovery from acute illness, several studies show that higher long-term mortality is independent of baseline functional and health status.⁷⁴

Adverse long-term outcomes are not limited to increased mortality risk. For example, elderly survivors of severe sepsis are up to three times as likely to develop persistent cognitive and functional impairments compared with elderly controls not hospitalized for sepsis.⁷⁵ Acute infections may worsen pre-existing chronic diseases or new chronic diseases may emerge. The relationship between acute infection and chronic illness may be bidirectional. Whereas the increased burden of chronic health conditions increase the risk of infection and sepsis, survivors of infection may develop a higher burden of chronic disease. For example, individuals with renal disease are at higher risk for serious infection. The episode of serious infection can lead to renal failure and eventually lead to chronic dialysis. Similarly, it has been shown that infection with influenza is associated with increased risk of cardiovascular disease. These examples underscore the complex relationship between infection and underlying chronic disease, where co-morbid conditions are both a risk factor and are modified by the infectious event. The worsening of chronic illness following infection is in turn a risk factor for subsequent acute illness, thereby initiating a spiral of events that can ultimately lead to death.

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Mechanisms underlying increased long-term mortality and morbidity remain unclear. Unresolved immune response during recovery may worsen long-term outcomes. For example, higher circulating levels of inflammatory and coagulation markers were observed at hospital discharge when patients appeared to have clinically recovered from infection and increased subsequent mortality.⁷⁶

Conclusion

Sepsis and severe sepsis are leading causes of death in the United States and the most common cause of death among critically ill patients in non-coronary intensive care units. Recent studies also suggest that acute infections worsen pre-existing chronic diseases or result in new chronic diseases, hence leading to poor long-term outcomes in acute illness survivors. People of older age, male gender, black race, and preexisting chronic health conditions are particularly prone to develop severe sepsis, hence prevention strategies should be targeted at these vulnerable populations. The epidemiology of severe sepsis in developing countries may differ significantly from developed countries, which warrants greater attention in future studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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