Long-term Outcomes from Sepsis

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Long-term mortality following severe sepsis is high, and fewer than half of patients who experience severe sepsis are alive at 1 year. Mechanisms underlying increased long-term mortality remain poorly understood. Animal and human studies suggest that abnormalities of the innate immune system may contribute to increased long-term mortality. This review article examines the epidemiology and potential mechanisms underlying long-term outcomes from sepsis and challenges to conducting long-term outcome studies in the critically ill.

Introduction

The traditional focus of critical care is to reduce short-term mortality, but in recent years, interest in understanding the impact of critical illness on long-term outcomes has increased [1]. Studies examining long-term outcomes of severe sepsis, acute lung injury, and lung transplantation suggest that critical illness is associated with long-term consequences that persist beyond intensive care unit (ICU) and hospital stay. These findings raise an important concern: Are advances in ICU care merely shifting the burden of illness from the acute care to the chronic care setting? Furthermore, our understanding of the long-term consequences is limited by the complex relationship between acute and chronic illness. Critically ill patients also have a high burden of comorbid conditions prior to the illness. Teasing out the effects of critical illness from chronic health conditions that predispose to an acute illness is difficult.

This review article examines the epidemiology and potential mechanisms of long-term outcomes of infection and sepsis. We have used sepsis as a model to understand critical illness, because its incidence is high and it is the most common cause of death in the noncoronary ICU. The article focuses on mortality as an outcome measure and provides a brief overview of other outcome measures.

Why Examine Long-term Mortality?

Considerable debate exists about the most appropriate time to assess outcomes in critical care. Over the past few years, a shift has occurred in examining outcomes, particularly mortality, at prespecified time points after admission to the ICU, rather than relying on ICU or hospital mortality alone. For instance, the International Sepsis Consensus Conference recommended using 90-day mortality [2]. Fixed time points are used for measuring mortality because different physicians have different criteria to discharge patients from the ICU or the hospital. In addition, due to the increasing cost of hospital services, physicians are often forced to discharge patients to other settings, such as skilled nursing facilities, residential care facilities, and ventilator rehabilitation facilities, often within the hospital premises. These patients frequently require rehospitalization and have poor outcomes, which would be ignored if outcomes were measured at hospital discharge alone.

Recent studies suggest that even 90-day mortality may be inappropriate for some critical illnesses that require prolonged hospitalization. For instance, a fourth of subjects enrolled in the acute respiratory distress syndrome (ARDS) network study to assess the efficacy of corticosteroids were still hospitalized at 60 days [3], suggesting that long-term follow-up is necessary to include events occurring during the hospitalization.

The most important goal of long-term studies of sepsis is to assess long-term consequences, particularly events occurring after hospital discharge. In a landmark study, Quartin et al. [4] showed that survival of sepsis patients is lower compared to controls from the general population 8 years following the initial hospitalization. Fewer than half and a fourth of patients who developed sepsis were alive at 1 and 8 years, respectively. The poor survival persisted when multivariable analysis was conducted to adjust for prehospitalization comorbid conditions. Several other studies have subsequently shown that mortality remains high for several years among hospital survivors of infectious diseases and sepsis [5–9,10•].

Another important reason to understand long-term outcomes is to account for long-term costs. An intervention that shifts mortality from the short term to the long term may increase costs substantially due to increased burden of providing long-term care. Conversely, an expensive intervention may be justified if it reduces both short- and long-term mortality. Therefore, understanding long-term consequences of sepsis has important public health implications.

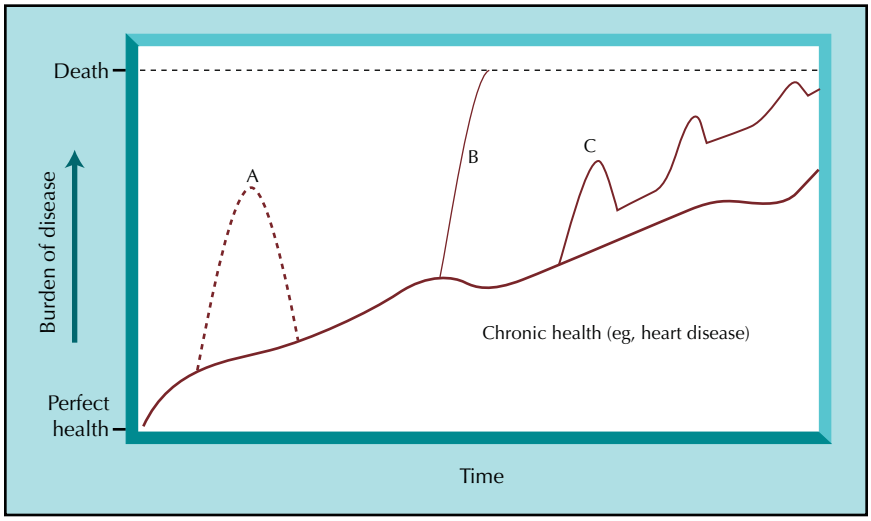

Figure 1. Conceptual model of the relationship of chronic disease and acute illness. Three outcomes follow severe sepsis: **A**, complete recovery; **B**, death during hospital stay; and **C**, partial recovery and increased burden of organ dysfunction at discharge, followed by multiple acute events, eventually leading to death.

Relationship between Acute and Chronic Illness

Often, the increased long-term mortality following infection and sepsis is perceived to be solely due to factors that place individuals at higher risk for these illnesses. When multivariable analyses were used to compare long-term mortality estimates, with and without chronic health conditions, the long-term estimates remained unchanged [5,7,10•]. These results suggest that the influence of chronic health conditions on long-term survival is small and that the acute illness is more likely to contribute to increased long-term mortality.

The relationship between acute and chronic illnesses is bidirectional. Increased burden of chronic health conditions increases risk of infection and sepsis, but survivors of severe sepsis may develop higher burden of chronic disease. To illustrate this point, individuals with renal insufficiency are at higher risk for infection and severe sepsis. Furthermore, the renal failure may worsen during the episode of severe sepsis, eventually requiring chronic dialysis. This example underscores the complex relationship between sepsis and comorbid conditions, where comorbid conditions are both a risk factor and modified by the sepsis event. The increased burden of comorbid conditions following sepsis is in turn a risk factor for subsequent acute illnesses, thereby initiating a spiral of events that eventually leads to death (Fig. 1).

Conceptual Model

Figure 1 is a conceptual model of long-term outcomes following infection and sepsis. Individuals with high burden of chronic health conditions are at increased risk of infection and sepsis. Three potential outcomes are possible following hospitalization for infection and sepsis. Approximately one fourth of severe sepsis patients die during the hospitalization. The remaining patients who are discharged alive either recover completely or experience incomplete recovery. Those with incomplete recovery are at increased risk of subsequent acute illnesses, which eventually leads to death.

Our conceptual model is supported by studies examining causes of rehospitalization and death in pneumonia survivors [5,10•]. For example, we recently showed that patients hospitalized with community-acquired pneumonia (CAP) have high risk of rehospitalization due to repeat infections and noninfectious reasons. The common noninfectious reasons include cardiovascular disease, such as ischemic heart disease, myocardial infarction, cerebrovascular disease, and congestive heart failure; exacerbation of chronic obstructive lung disease; and cancer. Interestingly, Mortensen et al. [11] showed that patients with pneumonia died due to the same reasons over a period of 90 days. These results provide important insights to explore mechanisms underlying increased long-term mortality after infection and sepsis.

Mechanisms

The innate immune response plays a vital role in resistance to infectious disease. Components of the innate immune response form the first line of defense in the recognition and destruction of pathogens, and cross-talk between the innate and acquired immune responses activates the acquired immune system. The innate response to infection sets into motion cellular and molecular events that account for the clinical manifestations and organ dysfunction during severe sepsis. Whether severe sepsis occurs due to uncontrolled inflammation or immune suppression is unclear [12], but these abnormalities of the innate immune response may also play a causal role in long-term outcomes of severe sepsis.

Several lines of evidence suggest that consequences of severe sepsis could be due to immune suppression. In a murine model of severe sepsis, using the cecal ligation and puncture method, mice were at higher risk for *Aspergillus fumigatus* and *Pseudomonas aeruginosa* reinfection when compared to mice undergoing sham

surgery. Mortality was 100% when mice were challenged with *Aspergillus* up to 15 days after the initial surgery. Although the exact mechanism for increased susceptibility to infections is unclear, impaired neutrophil function appeared to play an important role [13]. In humans, repeat infections are also common among survivors of infection and sepsis [10•]. For example, rehospitalization for a second episode of pneumonia was the most common cause of rehospitalization in subjects hospitalized initially for CAP. These results suggest that increased susceptibility to infections due to immune suppression could increase long-term mortality after severe sepsis. The exact mechanisms underlying increased susceptibility to reinfections remain unclear.

Preliminary work by our group suggests that upregulated proinflammatory markers could increase mortality after infection. Survivors of CAP have increased circulating concentrations of proinflammatory markers, such as interleukin (IL)-6, at hospital discharge [14]. Circulating IL-6 concentrations were threefold higher compared to apparently healthy individuals at risk for CAP, suggesting that uncontrolled inflammation may persist at discharge. Higher concentrations of IL-6 were associated with increased risk of death over 3 months. A common theme of these results is that immune dysfunction, commonly observed in severe sepsis patients, may persist at hospital discharge and influence long-term outcomes.

Outcomes other than Mortality

One or more organ dysfunction occurs during severe sepsis, and the frequency and severity of organ failure are the most important predictors of mortality during hospital stay. Whether these organ failures persist after discharge is unknown. Mortality is an important outcome and discussed in detail in the preceding section, but long-term assessment should also include other outcomes. These outcomes are important because they may increase risk of death and reduce quality of life. A comprehensive review of each outcome measure is beyond the scope of this article, and important review articles addressing these measures are listed [15–17].

Neurologic impairments

Neurologic complications are common in the critically ill. Abnormalities of cognitive processes such as perception, attention, problem solving, language (speaking and writing), and comprehension (listening and reading) are present in 25% to 78% of cases. Although studies examining long-term neurocognitive changes in sepsis survivors are not available, this complication has been extensively examined in ARDS and general medical ICU survivors [18,19]. For instance, in a study of ARDS survivors, 75% had neurocognitive deficits at 6 months, and 45% had similar deficits at 1 year. There was minimal recovery from 1 to 5 years. Neuropsychologic batteries used to assess cognitive deficits last up to 2 hours and require experienced personnel.

Respiratory impairment

Mechanical ventilation is common during severe sepsis, and ARDS is one of the most devastating complications in these patients. Respiratory impairment is an important cause of reduced exercise capacity and poor quality of life. Common methods to assess respiratory function include spirometry-based assessment of forced expiratory volume in the first second, forced expiratory volume, and diffusion capacity. Though pulmonary function tests can also be performed to more accurately assess restrictive lung disease common in ARDS, spirometry has practical advantages. It is easier to perform, especially in older subjects, and a portable spirometer can be transported easily. In addition to pulmonary function assessment, the need for home oxygen or the decline in oxygen saturation following exercise can be used to identify individuals with gas exchange abnormalities. These measurements are less sensitive, but they identify individuals with the greatest respiratory impairments. Finally, structural abnormalities of the lung can be ascertained by serial chest radiographs. Although a systematic assessment of the lung function in survivors of severe sepsis has not been conducted, long-term follow-up studies have examined changes in lung function in ARDS survivors. For instance, Herridge et al. [20] showed that functional and structural impairments in lung function are common during the initial 3 months, and most patients experience complete recovery by 1 year.

Renal failure

The prevalence of renal failure in critically ill patients varies between 3% and 25%. Most studies have reported high in-hospital mortality. Only one study has examined the course of renal failure in hospital survivors [21]. A German study examined outcomes of 979 ICU patients who developed renal failure. Although two thirds of these subjects died during the hospital course, survival after hospital discharge was better. Of the 301 subjects discharged alive, 69% and 50% survived at 6 months and 5 years, respectively. Only 10% required chronic dialysis, and more than half of the remaining patients had complete recovery of their renal function. However, an important limitation of this study was incomplete follow-up, available in only half the subjects discharged from the hospital.

Quality of life

Quality-of-life instruments, such as the Short Form-36 score and EuroQOL, have been commonly used to assess quality of life in long-term outcomes studies. For instance, Chelluri et al. [22] showed that quality of life was low 1 year after discharge in critically ill individuals who received mechanical ventilation. The incidence of disability is also very high, especially among older survivors who had disability prior to critical illness. The

increased incidence of disability is also associated with higher incidence of depression.

More than half of survivors of critical illness required caregiver support at 1 year. Although caregiver burden is well recognized in dementia, few studies have examined this issue in patients recovering from critical illness. For example, a recent study by Van Pelt et al. [23•] showed that caregivers have high incidence of depression, unemployment, and disruption of lifestyle at 1 year. Therefore, the consequences of severe sepsis affect not only the patient but also family members and caregivers.

Critical illness affects every organ system, such as changes in body weight, loss of skeletal muscle mass, and anemia. Trajectories of recovery of each of these abnormalities will vary. Results from ARDS and critically ill patients suggest that for most domains the recovery plateaus at 1 year. However, few studies have conducted detailed assessment beyond 1 year. The effect of sepsis on several domains remains poorly studied, and their effects on mortality are complex and poorly understood.

Design Challenges of Long-term Outcomes Studies

There are several challenges to examining long-term outcomes of sepsis, and these issues should be recognized when designing future studies.

Relationship between acute and chronic illness

The complex relationship between sepsis and pre-existing chronic illness presents unique challenges for designing studies of long-term outcomes of sepsis. A common problem is the choice of controls with which to compare outcomes of sepsis survivors. Recruiting large inception cohorts, conducting periodic assessments of chronic health conditions in the entire cohort, and following these individuals over time for occurrence of sepsis and its long-term sequelae is not practical. Therefore, a case-control approach is used. However, the strategy of comparing these sepsis survivors to healthy control subjects would be inappropriate, because it cannot differentiate between the effects of sepsis and the influence of pre-existing health conditions prior to the occurrence of sepsis. Using subjects from existing cohorts such as the Framingham study and matching them based on pre-existing chronic health conditions should be considered.

Analyzing informative censoring

Another challenge when assessing long-term outcomes of sepsis is informative censoring. Patients who die early do not contribute to subsequent nonmortality data, such as quality of life assessment. These patients are very sick prior to the illness and/or as a result of the illness, and they would have the worst quality of life during recovery. An intervention that improves short-term mortality may therefore worsen quality of life, whereas an intervention that worsens short-term mortality may appear to improve it. Statistical methods that account for competing mortality can be used to account for informative censoring.

Difficulties in follow-up in the outpatient setting

Study subjects have to return to follow-up clinics to participate in long-term outcomes studies. This poses several challenges. First of all, patients who fail to return to the clinic for follow-up are often the sickest; therefore, every attempt should be made to complete assessment for each survivor. In addition, sepsis survivors are often in nursing homes, long-term care settings, or other chronic care facilities. These subjects are frequently lost to follow-up, unless substantial efforts are made to track them. Alternate methods to complete assessment, such as home visits or telephone assessment, should be considered for these patients.

Interventions

There is no doubt that a better understanding of the long-term consequences of all interventions in the ICU will help physicians choose optimal therapies. However, an area that is gaining intense interest is whether sepsis survivors can be targeted for specific interventions at hospital discharge. For instance, patients are at higher risk for myocardial infarction and acute coronary syndromes. Aspirin, β-blocker, and statin therapy in these individuals may improve outcomes.

Conclusions

Long-term outcome studies of sepsis have shown its association with increased mortality for several years after the initial event. Our current understanding of the risk factors and mechanisms underlying long-term sequelae is limited. Identifying risk factors during the ICU course that influence long-term outcomes will help physicians choose better treatment options. At hospital discharge, predicting risk of poor outcomes will be important to target future interventions. A comprehensive approach, including genomics, proteomics, improved statistical methodology, and immune function assessment, could be incorporated to better understand mechanisms and develop sophisticated risk prediction models.

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