Is the mortality rate for septic shock really decreasing?

Eirini Christaki and Steven M. Opal

The Infectious Disease Division, the Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Correspondence to Steven M. Opal, MD, Memorial Hospital of RI, 111 Brewster Street, Pawtucket, RI 02860, USA
Tel: +1 401 729 2545; fax: +1 401 729 2795; e-mail: Steven_Opal@brown.edu

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Purpose of review

To critically examine the mortality rates of septic shock over the last 25 years to determine if significant improvements have been accomplished.

Recent findings

A gradual and progressive improvement in mortality rates associated with septic shock has been realized over the few decades. These improvements in outcome are quantitatively small but significant and they primarily represent improvements in supportive care, and the recognition that well meaning and seemingly logical treatments have been overused and probably contributed to excess mortality rates in the past.

Summary

Survival rates for patients in septic shock have gradually improved in critical care units worldwide over the last 25 years. Further improvement will be predicated on the discovery of new therapies to disrupt the underlying pathophysiology of sepsis and the development of improved rapid, diagnostic testing and immune monitoring of individual patients.

Keywords

bacteremia, sepsis, septic shock, survival rates

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Introduction

The management of septic shock remains a significant challenge to critical care specialists. Despite introduction of novel interventions in the management of sepsis (recombinant human activated protein C (PC) [1•], stress-dose corticosteroids [2•] and tight glycemic control [3•]), mortality rates remain disturbingly high. A review of existing evidence indicates that modest improvements in survival rates in severe sepsis/septic shock have occurred over the past two decades, but there is considerable room for improvement.

Much of the progressive reduction in mortality rates for septic shock is related to improved supportive care, protocolized systems for the rapid and appropriate use of treatment interventions, and prevention of iatrogenic complications [4•]. Simple maneuvers to prevent aspiration pneumonia, stress ulcer, deep venous thrombosis, and catheter-related infections have been of significant benefit to patients. Further improvements in outcome in septic shock will likely be difficult unless innovative use of personalized medicine and novel methods to disrupt the underlying pathophysiology of sepsis are developed [5•]. In this brief review, we summarize the overall outcomes for patients with septic shock over the last 25 years, and analyze the potential impact of various interventions responsible for these favorable trends in survival from septic shock.

Evidence of improved outcome in patients with severe sepsis/septic shock

We reviewed the literature on sepsis mortality trends published both nationally and internationally in the last 15 years and further examined these trends in specific populations.

Epidemiologic studies of secular trends and mortality rates in septic shock

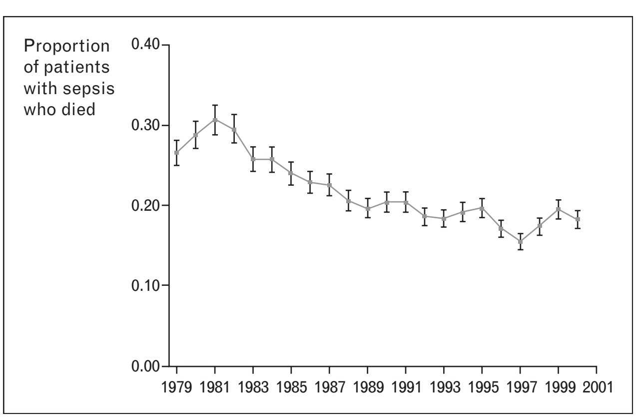
The estimated overall hospital mortality due to severe sepsis was 28.6% in a multicenter study from seven large states in the United States of America encompassing 192 980 cases. Mortality significantly increased with age, being 10% in children and 38.4% in those more than 85 years old [6]. Although the risk for sepsis was higher among men, after adjusting for age, site of infection and comorbidity, there was no significant difference in the risk of death between men and women with sepsis [6,7]. In a multicenter study, including 28 ICUs in six European countries, Canada and Israel between 1997 and 1998 the investigators found that ICU and hospital mortality rates were greater in patients with sepsis from hospital-acquired infection than in those with a community-acquired infection [8].

Multiple factors like age, gender, race, type and site of infection, preexisting comorbid conditions, number of organ system failure and underlying immune status, play a role in determining mortality in sepsis [6,7,9,10]. Prompt initiation of antibiotics within the first hour of presentation with severe sepsis, rapid fluid resuscitation, protective ventilation, tight glycemic control and early goal-oriented therapy, have all been shown to improve survival [11,12]. We investigated whether the advances in sepsis therapy have correlated with a decrease in overall mortality over the last 25 years.

In a review article about mortality from sepsis, the authors performed a meta-analysis and found a significant trend for improved survival in patients with septic shock between 1957 and 1997. The mortality rate had dropped from 61.6% in late 1980s to 53.1% ($P < 0.05$) a decade later [13].

Over the last three decades the incidence of sepsis in the USA has increased, yet the mortality rate has declined (Fig. 1). Based on the epidemiologic review of more than 10 million sepsis cases from the National Hospital Discharge Survey (NHDS) between 1979 and 2000, it was found that the incidence of sepsis has almost tripled, from 82.7 cases per 100 000 population in 1979 to 240.4 per 100 000 population in 2000. This trend was more evident in the first decade of the study period between 1979 and 1989. The same study showed that hospital mortality rates due to sepsis have decreased approximately 10% over the 22-year study period, from 27.8% in the early 1980s to 17.9% during the late 1990s ($P < 0.001$). Nevertheless, the absolute number of deaths due to sepsis increased three-fold (from 21.9 to 43.9 deaths per 100 000 population, $P < 0.001$) The incidence of septic patients with any organ failure also increased from 19.1% between 1979 and 1989 to 30.2% at the end of the study period pointing to a greater severity of illness among sepsis patients. The incidence of sepsis due to Gram-negative organisms has decreased whereas this incidence has not been demonstrated for Gram-positive pathogens [7]. Factors like the older age of patients with sepsis [14], the development of potent immunosuppressive and chemotherapeutic agents, advances in transplant medicine and the AIDS epidemic may have contributed to the increase in sepsis from 1979 to 2000.

Figure 1 The deceasing mortality rates for sepsis over the past 22 years in the United States



Adapted with permission from [7].

In another study by Annane *et al.* [10] data were extracted from the College des Utilisateurs de Bases de donnees en Reanimation (CUB-Rea) Network in France, including more than 100 000 ICU admissions in 22 hospitals over an 8-year period from 1993 to 2000. The results again showed an increase in the incidence of septic shock from seven per 100 admissions in 1993 to 9.7 per 100 admissions in 2000 but a decline in overall mortality from 62.1% to 55.9% ($P = 0.001$) respectively. Notably, the site of infection related with septic shock had changed with a progressive increase in pulmonary infections and a decline in urinary tract infections. Polymicrobial infections and multiresistant bacteria were also increasingly related to septic shock.

According to the bi-national Australian and New Zealand Intensive Care Society adult patient database there has been a 4% decline in risk-adjusted overall hospital mortality in patients admitted to the ICU between 1993 and 2003. The data included 223 129 patients from 99 ICUs and overall mortality was 16.1%. Most significant decrease was noted in the private and tertiary ICUs than in the metropolitan and rural ones. A decline in mortality rates was also noted in ICU ventilated patients over these 11 years [15•]. Although these results refer to both septic and nonseptic ICU patients, they reveal an important trend, as septic shock is one of the leading causes of death in the ICU.

Not all the studies in the literature support the same favorable trends in mortality. In a study of patients with ARDS (acute respiratory distress syndrome), despite a significantly decreasing overall mortality rate (approximately 30% reduction in ARDS mortality between 1980 and 1998), the case fatality of patients with sepsis and ARDS had not changed. The decline in mortality was mostly accounted for an improvement in survival of trauma patients and those with other risk factors for ARDS [16]. One limitation of the studies that have used national databases from hospital coding and discharge data is that they often can only assess crude morality rates, and not specific mortality rates attributable to sepsis.

Improved outcomes in selected populations of septic patients

Perhaps the most impressive improvements in outcome from severe sepsis and septic shock have been accomplished in specific populations of vulnerable patients as

Table 1 Improved outcomes in selected patient populations with severe sepsis/septic shock

Special group	Specific features	Improvements in management
Pediatric patients	Perinatal infections and complications, primary immunodeficiencies, congenital abnormalities	Prenatal monitoring and intrapartum prophylaxis, selective use of ECMO and polyclonal immunoglobulin therapy in neonatal sepsis, specialized neonatal and pediatric units
Elderly patients	Multiple underlying conditions; immunosenescence, poor physiologic reserve	Skilled ICU support improves outcome in elderly, realistic limitation of care when appropriate
Neutropenic cancer patients	Increased risk of fungal and other opportunistic infections, diagnostic challenges, bleeding risk	Selective use of G-CSF, avoidance of severe myelotoxic chemotherapy regimens, improved diagnosis and treatment for fungal sepsis, Hematopoietic stem cell transplantation has improved bone marrow recovery and outcomes
Trauma and burn patients	Initial insult causes immune dysfunction; risk of secondary infection; difficulty in diagnosis of sepsis	Specialized burn and trauma units, improved burn wound management, selective use of growth factors
HIV infections	Excess risk of Gram-positive bacterial sepsis, opportunistic infections, multiple infections; immune reconstitution syndromes	Current antiretroviral regimens have greatly improved outcomes in HIV patients needing critical care for septic shock

ECMO, extracorporal membrane oxygenation; G-CSF, granulocyte colony stimulating factor; HIV, human immunodeficiency virus; ICU, intensive care unit.

summarized in the following paragraphs. Table 1 highlights these special groups of septic patients.

Cancer patients

Cancer patients have a greater risk for severe sepsis than the general population, probably related to immunosuppression caused by the malignancy itself or its treatment. According to a multicenter study involving 606 176 cancer hospitalizations, cancer patients were four times more likely to be hospitalized with severe sepsis (relative risk 3.96; 95% CI, 3.94–3.99) than noncancer patients. Overall hospital mortality for patients with malignancy and severe sepsis was 37.8% compared with 24.9% of septic patients without neoplasia. Similar higher trends were noted for length of stay and hospitalization costs of cancer patients [17].

Pène *et al.* [18•] examined the trend in mortality rates between cancer patients with septic shock admitted to the ICU at the period 1998–2001 ($n = 90$) and 2002–2005 ($n = 148$). The 28-day survival rates were 27.8% in the first group and 47.3% in the second ($P = 0.003$) and ICU and hospital survival rates were 26.7 versus 41.2% ($P = 0.02$) and 21.1 versus 36.5% ($P = 0.01$) respectively [18•]. Additionally, a study by Larche *et al.* [19], with more than half of the patients having neutropenia, the overall 30-day mortality in critically ill patients with malignancy decreased from 79.4% during 1995–1997 to 55.5% during 1998–2000 [19].

These findings are also supported by another study of more than 1.7 million cases of cancer patients with sepsis from the National Hospital Discharge Survey (NHDS) where the case fatality was found to have decreased from 44.7 to 23.8% ($P < 0.001$) between 1979 and 2001. Interestingly, this mortality trend was more obvious among Gram-negative infections (48.2 to 13.2%, $P < 0.001$) [20].

Elderly patients

More than 60% of the sepsis patients in the USA are 65 years or older [6] and these patients have a greater risk of death that younger individuals [adjusted odds ratio (OR), 2.26; confidence interval (CI) 2.17–2.36] [14]. It was shown recently that in a group of septic patients more than 65 years old in a tertiary hospital, the 28-day mortality was significantly decreased (39 vs. 55% in the control group) when the sepsis 'bundle' protocol (early goal directed therapy, intensive insulin therapy, hydrocortisone supplementation, and drotrecogin alfa infusion assessment) was implemented [21•]. Thus, aggressive management of septic elderly patients in the ICU should be considered when deemed appropriate. Mortality rates due to sepsis in the elderly population have declined faster over time than the less than 65 years old cohort in the NHDS data from 1979–2001 [14].

HIV patients

HIV/AIDS patients with severe sepsis have greater mortality than non-HIV/AIDS septic patients (29 versus 20% respectively, $P < 0.0001$) [22]. Fortunately, in the era of highly active antiretroviral therapy (HAART) the survival of patients with HIV and AIDS has significantly improved. Although there are conflicting data on the mortality trend in the HIV patients admitted to the ICU in the post-HAART period, admissions secondary to respiratory failure and opportunistic infections have decreased. HIV patients are now more likely to be admitted to the ICU for non-HIV-related diseases, including sepsis [23].

Pediatric patients

Severe sepsis remains an important contributor of pediatric morbidity and mortality and is often related to perinatal complications, primary immunodeficiencies, and malignancy in childhood and trauma. After reviewing 21 448 hospitalizations for severe sepsis using the Kids' Inpatient database, Odetola *et al.* [24•] concluded that the overall in hospital mortality was 4.2%. More than two-thirds of the hospitalized children were either less than 5 years old or between 15–19 years of age. Mortality was significantly associated with the number of comorbid illnesses, the severity of illness and the number of failing organ systems.

Advances in the critical management of pediatric patients with sepsis include the prompt initiation of antibiotics and adequate fluid resuscitation, the use of inotropic agents, hydrocortisone, immunoglobulin and extracorporeal membrane oxygenation (ECMO) in neonates [25]. Advances in hematopoietic stem cell transplantation have contributed to the greater survival of pediatric patients with malignancies at risk for sepsis [26•].

Burn and trauma patients

Trauma and burn patients are at risk of acquiring a secondary infection and progressing to sepsis as well as at a greater risk for developing acute lung injury. Our better understanding of wound management, trauma care and the use of protective ventilation strategies, with other supportive measures in the ICU, have contributed to a significant decrease in mortality attributed to ARDS [16]. Major advances towards more rapid and specialized care of these patients in dedicated trauma and burn units have dramatically affected their survival [27].

Specific elements of improved supportive care in septic patients

Supportive care for critically ill patients with septic shock is improving. A summary of the most important elements that account for improved outcomes is provided in Table 2.

Fluid management and hemodynamic monitoring

There is reasonably compelling evidence to support the widespread use of early goal directed therapy in the treatment of septic shock [28–30]. This vigorous resuscitation method, used in a standardized fashion with specifically defined, clinical and physiological endpoints, is feasible and likely to result in improved survival. This resuscitative strategy more rapidly restores the systemic circulation and tissue perfusion to patients in septic shock than standard care measures in emergency departments. Early goal directed therapy, along with reports indicating its lack of clinical utility, has reduced the use of pulmonary artery catheters in favor of central venous pressure monitoring [29–31].

The choice of intravenous fluid (colloid versus crystalloid) does not appear to be a major determinant in outcome in septic shock [32], and the use of artificial plasma expanders such as pentastarch should be avoided [3•]. The type of vasopressor agent used to support the blood pressure (BP) in septic shock is largely dependent on the experience and preferences of the clinician [33]. Norepinephrine and dopamine are generally the preferred agents at present [28,33], but a recent, controlled, clinical trial suggests epinephrine may be as effective and safe as norepinephrine and dobutamine [34•]. Vasopressin is a potent vasoactive hormone that is increasingly used in the management of septic shock [35]. Yet, a recent clinical study found vasopressin to be no more effective than catecholamines, except perhaps for some improvement in less severely hypotensive patients [36•].

Following the initial resuscitation and stabilization of the patient's hemodynamics, patients with septic should be

Table 2 Improvements in the supportive care and management of septic shock

Parameter	Improvements	Outcome effects
Fluid therapy	Early goal-directed resuscitation; restricted fluid management after shock reversal, judicious use of norepinephrine, vasopressin, and other vasopressors and inotropic agents	Standard protocols for fluid therapy with physiologic endpoints improve outcome
Infection prevention	Semirecumbent positioning, less use of pulmonary artery catheters, improved catheter design and care, selective use of SDD	Less aspiration pneumonia, less catheter-related infections
Ventilatory support	Low tidal volume ventilation, prone positioning, weaning protocols, better oxygen monitoring, avoid paralyzing agents during mechanical ventilation, daily testing for sedation needs and weaning efforts	Less over stretched alveoli, less local damage and systemic inflammation, shorter time on ventilator
Glycemic control	Tight glucose control with intensive insulin use	Improved cellular function, possibly reduced infection risk
Blood and platelet support	Lower RBC transfusion thresholds Less exposure to platelet transfusions	Lower transfusion risk, reduced transfusion-related hemodynamic and immunologic dysfunction
Nutritional support	Greater reliance on early enteral feeding, nutritional monitoring	Less use of central venous alimentation, lower infections, improved nutritional support
Antibiotics	Give appropriate antibiotics within 1–2 h of onset of septic shock, antibiotic de-escalation strategies, targeted therapy, short-duration antibiotic use	Lower mortality rate, lower antibiotic resistance rates
Renal support	Start renal support strategies early, improved efficiency membranes and improved blood flow devices and anticoagulation methods	Improved fluid and electrolyte management
Protocolized care	Use standardized physiologic end points for fluids and ventilation, blood products, thromboprophylaxis, stress ulcer prevention, etc.	Protocolized, sepsis 'bundles' improve outcomes

RBC, red blood cell; SDD, selective decontamination of the digestive tract.

managed with limited intravenous fluids once the BP has been fully restored. There has been a longstanding debate about high volume maintenance fluids versus low volume fluids after the initial phase of the management in septic shock [37].

Proponents of the high volume (or 'liberal') maintenance fluids argue that myocardial dysfunction of sepsis requires a higher preload to maintain adequate cardiac outputs and this approach improves tissue perfusion and renal function. Opponents of this view have emphasized that interstitial and pulmonary edema with impaired oxygenation accompanies excess fluid administration in septic patients. They argue in favor of a low volume ('conservative') fluid management strategy. These two strategies directly tested in a prospective clinical trial by Weidemann *et al.* [37]. The low volume strategy resulted in shorter time required for mechanical ventilation with no impairment of renal function. The conservative treatment group had a trend to improved hospital survival rates, but this difference did not reach statistical significance.

Antibiotic management and infection prevention

As with many other severe infectious diseases, early intervention with appropriate antimicrobial therapy provides a survival benefit in septic shock. Every hour delay in effective antimicrobial therapy increases the mortality rate from septic shock by 5–10% [12]. Similarly, early intervention with empiric antifungal chemotherapy in patients at high risk for candidal blood stream infections improves outcome [38].

Infection prevention in the ICU includes reduced use of pulmonary artery catheters and short duration use of intravenous catheters. Simple maneuvers, such as keeping the head of the bed up to prevent aspiration, optimal sterile technique with insertion and maintenance of catheters, improvements in catheter design and early removal of vascular and urinary catheters, all reduce secondary infections in patients requiring long ICU stays. Evidence to support the use of these measures has recently been reviewed [4•].

The specific role of selective decontamination of the digestive tract (SDD) in the management of patients with septic shock has never been adequately studied [4•]. SDD reduces the incidence of healthcare-associated pneumonia when universally applied in ICUs, particularly ventilator-associated pneumonia, without apparent risk of development of multidrug-resistant Gram-negative bacteria [39,40]. SDD primarily used as primary prevention against infection in high-risk surgical patients of the ICU. Its role in patients with established septic shock is unknown [4•].

Ventilatory support and tissue oxygenation

A major contribution to improved survival rates in septic patients has been the widespread adoption of low tidal volume ventilation strategies in patients with acute respiratory failure from septic shock. The acute respiratory distress syndrome network study [41] convincingly demonstrated that improved survival accrues from low tidal volume ventilation (6 mg/kg) versus high tidal ventilation (12 ml/kg) in the management of ARDS. This lung protection strategy is now generally accepted as the optimal ventilation strategy in ARDS [4•,42].

Various lung recruitment strategies to improve gas exchange during mechanical ventilation have been proposed, yet none has clearly achieved widespread success [43]. Positive end expiratory pressure (PEEP) should be set to avoid lung collapse at end of expiration. The optimal plateau pressures and amount of PEEP to provide adequate gas exchange limit lung injury and improve outcome remains unclear and is probably related to individual-patient characteristics [43]. Prone positioning with the use of low-volume pressure-limited ventilation probably improves survival in selected patients with severe ARDS [44]

Glycemic control and insulin requirements in septic shock

Tight glycemic control in critically ill patients in medical ICUs appears to be beneficial in reducing long-term mortality rates in patients with long ICU stays [45]. Excessive blood glucose levels may be injurious to cellular function and mitochondrial respiration and interferes with neutrophil clearing of microbial pathogens. Tight glycemic control is not without significant risks. A recent study [3•] failed to show improvement in outcome with intensive insulin therapy and resulted in increased hypoglycemic episodes in patients with severe sepsis. The Surviving Sepsis Campaign [4•] generally supports glycemic control but set the upper limit of acceptable blood sugar level at 150 mg/dl rather than 120 mg/dl.

Transfusion therapy

The potential hazards associated with the transfusion of stored red blood cells on the microcirculation, oxygen delivery and sequelae of transfused alloantigens is increasingly appreciated [46]. For these reasons, a transfusion threshold to maintain target hemoglobin of 7–9 g/dl (or 70–90 g/l) is now considered appropriate in the critical care unit [4•,47]. These recommendations apply to patients without evidence of ongoing coronary ischemia, severe hypoxemia, active bleeding, cyanotic heart disease or lactic acidosis. Reduced blood transfusion use in hospitalized patients might be one of the multiple reasons for improved outcomes in severe sepsis over the last two decades. The use of human recombinant erythropoietin has been shown to decrease red cell transfusion requirements but had no overall effect on clinical outcome in large, controlled trials in critically ill patients [48].

Renal replacement therapy

It is generally agreed that early institution of renal replacement therapy is warranted for the management of acute kidney injury in severe sepsis/septic shock. Although the precise timing and type of renal support strategy remains the subject of considerable controversy [49,50]. Dialysis equipment, hemodialysis and hemoperfusion membranes and flow characteristics of renal replacement techniques have considerably improved over the last 25 years. Standard intermittent renal replacement therapy performs as well as continuous venovenous hemofiltration in most studies [4•,49]. Continuous venovenous hemofiltration may be preferred in hemodynamically unstable patients with septic shock.

It has been argued that high-flow hemofiltration may provide additional survival benefits by removing inflammatory molecules such as circulating cytokines and chemokines from the circulation of septic patients [51]. The relative merits of various types of continuous versus intermittent hemofiltration and hemodialysis methodologies are under clinical investigation at the present time.

Conclusion

The mortality rate for septic shock has significantly decreased over the past two decades. This improved outlook is primarily attributable to innovations in supportive care and, equally important, to reduction in the use of nonbeneficial, or even harmful, therapies that were previously considered standard care for ICU patients with septic shock. As noted in a recent study of critically ill cancer patients with severe sepsis [18•], survival benefits have accrued from the combined impact of small increments in supportive care and avoidance of iatrogenic complications.

Further substantial improvements in sepsis management will be predicated upon the introduction of therapies that effect the fundamental pathophysiology of septic shock itself. Intelligent application of these innovative agents will need to individualize treatment regimens to the specific patient needs. The real time application of systems biology for each patient (i.e., 'personalized medicine') will probably be required if major improvement in sepsis care is to be realized in the future.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 618–619).

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