EDITORIAL



# Declining Case Fatality Rates for Severe Sepsis
## Good Data Bring Good News With Ambiguous Implications

Theodore J. Iwashyna, MD, PhD; Derek C. Angus, MD, MPH

**The medical literature** and the lay press often report substantial changes in the incidence or mortality of different diseases, including accounts of both large improvements in survival and warnings of burgeoning epidemics. If true, such information would be crucial for policy makers, patients, clinicians, and researchers. However, these reports can often be due to what Feinstein et al[1] dubbed the "Will Rogers phenomenon" (also known as stage migration), rather than real change. Feinstein and coauthors noted that, with increased awareness and more liberal diagnostic testing, patients with milder stages of cancer who were previously not identified were subsequently counted in an expanded denominator, resulting in an apparent increase in incidence, and because these new cases had less severe or less advanced disease, there was an apparent decrease in mortality. Teasing out real changes from the Will Rogers phenomenon requires an approach that is immune to changes in diagnosis over time. However, with increasing diagnostic testing, the risk of the Will Rogers phenomenon is substantial for some diseases and conditions.

Related article

One condition potentially susceptible to this phenomenon is severe sepsis, the syndrome of infection complicated by acute organ dysfunction. Following an initial estimate that there were 750 000 cases in the United States in 1996,[2] several groups subsequently reported the incidence was increasing precipitously,[3-6] with the National Center for Health Statistics ranking "septicemia" as the single most expensive reason for hospitalization in the United States in 2011.[7] At the same time, the case fatality rate from sepsis was reported to be declining.[3-6] One interpretation was that severe sepsis was becoming an increasingly large public health problem. At the same time, the hope was that advances in the care of severe sepsis were yielding important reductions in mortality. But is it true?

Critics rightly pointed out that these are not multiple independent confirmations of the decline in mortality from sepsis. Instead, these reports could be repeated replications of the Will Rogers phenomenon. Patients who were once labeled as "infection" with a concomitantly diagnosed acute organ dysfunction were now more likely to be labeled "severe sepsis."[8] These studies relied on codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification*, and new codes specifically for severe sepsis likely accelerated this change in coding. When infection with less severe physiologic derangements were instead classified as severe sepsis, those newly relabeled patients were less likely to die, expanding the denominator and decreasing the apparent mortality rate but not actually changing the outcomes for patients.

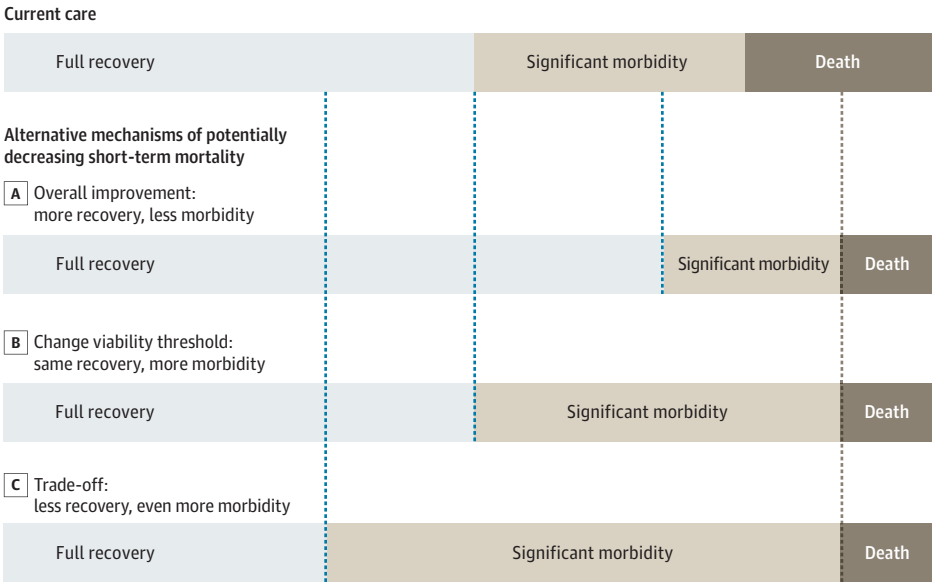
In this issue of *JAMA,* Kaukonen and colleagues[9] present a compelling epidemiologic study from Australia and New Zealand that overcomes many of the limitations of prior studies. Using a binational adult intensive care unit (ICU) registry of more than 1 million patients admitted from 2000 to 2012, the authors used a variety of strategies to determine the extent to which there were true changes in the epidemiology of severe sepsis admitted to the ICU.

First, Kaukonen et al report that the incidence of critically ill severe sepsis and septic shock increased in ICUs across Australia and New Zealand. Using the international consensus conference definition of severe sepsis,[10] they determined whether each patient was infected and whether synchronous organ dysfunction developed. The authors identified cases admitted for infection, regardless of whether patients were labeled "severe sepsis," and used objective definitions of acute organ dysfunction carefully abstracted at the bedside by nurse abstractors. The number of cases of severe sepsis and the proportion of severe sepsis or septic shock among all ICU admissions increased every year, from 7.2% (2708 of 35 012 ICU admissions) in 2000 to 11.1% (12 512 of 100 286 ICU admissions) in 2012.

Their findings were robust to sensitivity analyses, including restriction of the data set to the 63 ICUs that contributed data across all years. This suggests that the true incidence of severe sepsis throughout the community actually increased. However, increased awareness of severe sepsis could have led to different ICU admission thresholds, so these data only suggest, and do not prove, the increase in community incidence rates. Nonetheless, this is strong evidence that ICUs in Australia and New Zealand are admitting more patients from the community for severe sepsis.

Second, the authors report that hospital case fatality rates from severe sepsis have declined substantially over the study period, from 35% (949 deaths among 2708 patients) in 2000 to 18.4% (2300 deaths among 12 512 patients) in 2012. Using careful, objectively defined Acute Physiology and Chronic Health Evaluation (APACHE) III severity of illness scores abstracted and calculated consistently across the period, they demonstrate that, for the same degree of severity, mortality decreased every year from 2000 through 2012. Perhaps most strikingly, for young and middle-aged adults with little medical history of underlying illness (ie, the

Figure. Potential Mechanisms of Decreasing Short-term Mortality Among Patients Across a Distribution of Illness Severity




patients often considered ideal candidates for severe sepsis trials), mortality was considerably lower than 10% in 2012. Improvements in sepsis care in Australia and New Zealand also kept pace with other ongoing improvements in nonsepsis ICU care.

These findings have implications beyond sepsis care. The simplest is that, as clinicians struggle to improve care, the typical preintervention/postintervention evaluation of quality improvement (QI) efforts is often useless, unless accompanied by an "untreated" contemporaneous comparison group. That is, simply adjusting for the level of case fatality prior to a QI initiative, but not adjusting for the ongoing trajectory of improvement in care, yields no useful information from the analysis. Instead, this study strongly supports the need for so-called "difference-in-differences" evaluations to determine whether any improvement over time is larger (or not) in the intervention group than that in a control group not undergoing the specific QI intervention.

Another implication is the growing recognition of the inadequacy of short-term case fatality as an exclusive metric of outcome for severe sepsis. Although the decline in sepsis-related case fatality rates is a positive development, the recent history of critical care suggests that this decline can occur in many ways, with diverse implications for survivors. For instance, consider a distribution of patients across some measure of physiologic derangement reflecting severity of illness, with the assumptions that patients sicker than some mortality threshold die, those below that mortality threshold but above another threshold are debilitated, and the remaining patients achieve full recovery (**Figure**).

A reduction in short-term mortality could occur in 3 ways. Ideally, newer improved care could expand the domain of recovery, making all patients better off. Not only do more patients survive, but those who would have survived with debility also benefit (Figure). In a second model, short-term mortality could be improved simply by changing the viability threshold—the degree of severity of illness beyond which death is unavoidable. Such changes in care increase the number of seriously debilitated survivors while having no real effect on the outcome for the majority of survivors. As a third possibility, improvements in case fatality rate might have a mortality/morbidity trade-off. In such cases, achieving better short-term mortality involves exposing all patients to worsened morbidity. For example, aggressive bed rest and sedation in the ICU may prevent some exercise-induced cardiopulmonary decompensation, but at the risk of making all patients weaker and more delirious.[11-13] Even more dramatic examples of such paradoxical trade-offs may have occurred in decompressive craniotomy for diffuse traumatic brain injury.[14]

Thus, the study by Kaukonen et al[9] provides compelling evidence that recent claims about changes in severe sepsis mortality are not solely due to the Will Rogers phenomenon. Short-term mortality has declined to a level at which it no longer reflects the entire story of outcomes for patients with severe sepsis. Although the reduction in sepsis-related mortality is welcome, it makes the need for data on morbidity and longer-term outcomes all the more pressing. Even while awaiting confirmation of this mortality finding in other settings, the general challenge for research is clear. Clinical trials need to adopt longer-term morbidity measures, if only to have the power to be able to detect feasible effect sizes in new trials. Registries and benchmarking programs need to find low-cost ways to assess outcomes other than short-term mortality, if only to remain relevant. Critical care is improving for patients with severe sepsis and throughout the ICU, and clinicians and researchers must raise the standards and broaden measurement to continue such progress.

## ARTICLE INFORMATION

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Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

**IMPORTANCE** Severe sepsis and septic shock are major causes of mortality in intensive care unit (ICU) patients. It is unknown whether progress has been made in decreasing their mortality rate.

**OBJECTIVE** To describe changes in mortality for severe sepsis with and without shock in ICU patients.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective, observational study from 2000 to 2012 including 101 064 patients with severe sepsis from 171 ICUs with various patient case mix in Australia and New Zealand.

**MAIN OUTCOMES AND MEASURES** Hospital outcome (mortality and discharge to home, to other hospital, or to rehabilitation).

**RESULTS** Absolute mortality in severe sepsis decreased from 35.0% (95% CI, 33.2%-36.8%; 949/2708) to 18.4% (95% CI, 17.8%-19.0%; 2300/12 512; $P < .001$), representing an overall decrease of 16.7% (95% CI, 14.8%-18.6%), an annual rate of absolute decrease of 1.3%, and a relative risk reduction of 47.5% (95% CI, 44.1%-50.8%). After adjusted analysis, mortality decreased throughout the study period with an odds ratio (OR) of 0.49 (95% CI, 0.46-0.52) in 2012, using the year 2000 as the reference ($P < .001$). The annual decline in mortality did not differ significantly between patients with severe sepsis and those with all other diagnoses (OR, 0.94 [95% CI, 0.94-0.95] vs 0.94 [95% CI, 0.94-0.94]; $P = .37$). The annual increase in rates of discharge to home was significantly greater in patients with severe sepsis compared with all other diagnoses (OR, 1.03 [95% CI, 1.02-1.03] vs 1.01 [95% CI, 1.01-1.01]; $P < .001$). Conversely, the annual increase in the rate of patients discharged to rehabilitation facilities was significantly less in severe sepsis compared with all other diagnoses (OR, 1.08 [95% CI, 1.07-1.09] vs 1.09 [95% CI, 1.09-1.10]; $P < .001$). In the absence of comorbidities and older age, mortality was less than 5%.

**CONCLUSIONS AND RELEVANCE** In critically ill patients in Australia and New Zealand with severe sepsis with and without shock, there was a decrease in mortality from 2000 to 2012. These findings were accompanied by changes in the patterns of discharge to home, rehabilitation, and other hospitals.

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Editorial

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Severe sepsis and septic shock are the biggest cause of mortality in critically ill patients.[1,2] Over the last 20 years, multiple randomized controlled trials (RCTs) have attempted to identify new treatments to improve the survival of these patients. Earlier RCTs of activated protein C,[3] early goal-directed therapy,[4] and low-dose hydrocortisone[5] showed promise. However, later pivotal RCTs[6-15] and observational studies failed to confirm improvements in mortality or challenged their external validity.[16,17] Randomized controlled trials of antithrombin III,[6] tifacogin,[7] activated protein C,[8,9] vasoactive drugs,[10,12] hydrocortisone,[13] fludrocortisone,[14] intensive insulin therapy,[11,14] large-molecular-size hydroxyethyl starch,[11] and eritoran[15] all failed to improve mortality despite positive phase 2 studies and highly supportive animal studies. These failures have led to a sense that little progress has been made in decreasing the mortality of severe sepsis[18,19] and a view that improvements are unlikely. However, the accuracy of these negative views has not been tested in a large population of intensive care unit (ICU) patients with severe sepsis.

Accordingly, we sought to estimate trends in mortality in a large cohort of patients with severe sepsis from 2000 to 2012. We hypothesized that mortality rates have decreased significantly over the last decade.

## Methods

We conducted a retrospective study using data from the Australian and New Zealand Intensive Care Society adult ICU patient database[20] run by the Centre for Outcome and Resource Evaluation. The study was approved by the Alfred Hospital human research ethics committee, Melbourne, Australia, with a waiver of informed consent. Population data were retrieved from the Australian Bureau of Statistics[21] and Statistics New Zealand.[22]

### Description of Patients

We included all patients fulfilling the criteria of severe sepsis during a 13-year period from January 1, 2000, to December 31, 2012. For comparison, we estimated trends in outcome for all other patients in the adult patient database. We analyzed all hospital outcomes (mortality, discharge home, discharge to other hospital, and discharge to rehabilitation). Discharge to rehabilitation included discharge to rehabilitation facilities and chronic care facilities such as nursing homes.

Patients were analyzed in the following subgroups: presence of a comorbidity as defined by the Acute Physiology and Chronic Health Evaluation (APACHE) II[23] or APACHE III[24] classification system, severe sepsis, septic shock, medical admission, operative admission, respiratory failure, renal failure, APACHE II score 25 or greater,[3] APACHE III score quartiles (Q1 denotes the lowest score quartile and Q4 denotes the highest score quartile), age groups (≤44, 45-64, 65-84, ≥85 years), APACHE III admission diagnosis of sepsis (other than urinary tract infection), sepsis of urinary tract infection, sepsis with shock (other than urinary tract infection), and sepsis of urinary tract infection with shock. We further analyzed mortality in younger patients to evaluate its evolution in presumably previously healthy patients. Younger age was defined as 44 years or younger according to the APACHE systems.[23,24]

### Definition of Sepsis

We used the criteria for severe sepsis of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definition.[25] Organ failures were defined as a score of 3 or greater on the Sequential Organ Failure Assessment (SOFA)[26] except for cardiovascular failure (eMethods in the Supplement).

Severe sepsis with and without shock were defined by the presence of 2 or more systemic inflammatory response syndrome criteria within the first 24 hours after ICU admission and either (1) APACHE III admission diagnosis consistent with sepsis or (2) APACHE admission diagnosis consistent with infection accompanied by organ failure (eMethods in the Supplement):

1. APACHE III admission diagnosis consistent with sepsis:
   - A. Sepsis (other than urinary tract infection)
   - B. Sepsis of urinary tract infection
   - C. Sepsis with shock (other than urinary tract infection)
   - D. Sepsis with shock (urinary tract infection)
   - E. Severe sepsis: A and B
   - F. Septic shock: C and D
2. Infection and organ failure criteria:
   - A. APACHE admission diagnosis consistent with infection
   - B. At least 1 organ failure within the first 24 hours after ICU admission
   - C. Severe sepsis: A and any organ failure in B
   - D. Septic shock: A and cardiovascular organ failure in B

### Statistical Analysis

Data are presented as percentages and numbers, means with SDs, medians and interquartile ranges (IQRs), or proportions and 95% CIs. Accordingly, $\chi^2$ tests for equal proportion, *t* tests, or Wilcoxon rank sum tests were used to test differences.

To account for the change in incidence in severe sepsis over the duration of the study period, each patient's risk of presenting at ICU with severe sepsis (ie, risk of being septic) was determined using a logistic regression model (eMethods and eTable 1 in the Supplement).

To investigate the change in hospital outcomes over time for all ICU patients, logistic regression models were used, fitting main effects for severe sepsis, year of admission, APACHE III risk of death, and each patient's risk of being septic, with patients nested within site and site treated as a random effect. To ascertain if the change in outcome over time differed between severe sepsis and nonsepsis patients, an interaction term between severe sepsis and year of admission was fitted with year of admission treated first as a categorical variable and then as a continuous variable.

To more closely examine the change in hospital outcome over time, specifically among the severe sepsis population, a 3-stage multivariable modeling process was used. Full details of the analysis are presented in the eMethods in the Supplement.

All logistic regression results have been reported as odds ratios (ORs) and 95% CIs. Given a large database (>1 000 000 ICU patients, >100 000 sepsis patients), in order to more closely

align clinical and statistical significance, a 2-sided *P* value of .001 was used for variable inclusion and to indicate statistical significance.

To examine hospital length of stay for nonsurviving severe sepsis patients, length of stay was log-transformed and analyzed using mixed linear modeling, adjusting for patient severity and risk of being septic, with patients nested within site and site treated as a random effect. Results are reported as geometric means and 95% CI.

To ensure consistency of results across a stable population, sensitivity analysis was performed by repeating all analysis on a subpopulation of 63 hospitals that provided data for each of the 13 years of the study period. Statistical analysis was performed using SAS version 9.3 (SAS Institute).

## Results

Of 1 037 115 patients treated in 171 ICUs during the study period, 101 064 (9.7%) had severe sepsis, and 15 471 (15.3%) were of younger age (≤44 years). Comorbidities were present in 36 915 patients (36.5%). The median numbers of ICU and hospital beds were 5 (IQR, 3-10) and 200 (IQR, 134-330), respectively. The ICU and hospital bed availability is presented in eFigure 1 in the Supplement. The incidence of all ICU admission and ICU admissions with severe sepsis is presented in eFigure 2 in the Supplement. The proportion of severe sepsis admissions to all ICU admissions increased from 7.2% (2708/35 012) to 11.1% (12 512/100 286) (eFigure 2). The OR for admission with severe sepsis was 1.54 (95% CI, 1.47-1.61) in 2012 (year 2000 as reference). To account for the change in the incidence in severe sepsis, the risk of being septic was determined using a logistic regression model and confirmed to have increased (eTable 1).

### Mortality in Nonseptic Patients Over Study Period

Crude mortality decreased in all nonseptic patients (eFigure 3 in the Supplement). Adjusted mortality also decreased in nonseptic patients from 2000 to 2012 similarly to patients with severe sepsis (severe sepsis OR, 0.94 [95% CI, 0.94-0.95] vs nonsepsis OR, 0.94 [95% CI, 0.94-0.94]; *P* = .37).

### Crude Hospital Mortality in Severe Sepsis With or Without Shock

Baseline characteristics and outcomes of patients with severe sepsis are presented in **Table 1**. Over the entire study period, overall hospital mortality was 24.2% (95% CI, 23.9%-24.5%), but 33.1% (95% CI, 32.6%-33.6%) in patients with comorbidities and 19.1% (95% CI, 18.8%-19.4%) in those without (*P* < .001). Over the study period, mortality decreased from 35.0% (95% CI, 33.2%-36.8%; 949/2708) to 18.4% (95% CI, 17.8%-19.0%; 2300/12 512) (*P* < .001), an average annual decrease of 1.3% (**Figure 1** and **Table 2**). The changes in mortality in patients with severe sepsis and in severe sepsis subgroups are presented in Table 2.

### Crude Mortality in Younger Patients With Severe Sepsis With or Without Shock

The characteristics of younger patients (≤44 years, n = 15 471) are presented in eTable 2 in the Supplement. The changes in mortality in the subgroups of younger patients are presented in eTable 3 in the Supplement.

In 2012, mortality exceeded 15% in younger patients only in specific subgroups (eTable 3). Mortality exceeded 20% in 2012 only in younger patients with an APACHE II score of 25 or higher or within APACHE III quartile 4. In the absence of comorbidities and older age, mortality was less than 5% (eTable 3).

### Adjusted Mortality in Patients With Severe Sepsis

On logistic regression for mortality, the OR for mortality in all patients with severe sepsis was 0.49 (95% CI, 0.46-0.52) in 2012 using 2000 as reference. There were linear trends toward a decreased OR for mortality throughout the study period in all patients with severe sepsis as well as in all subgroups from year 2000 to year 2012 (*P* < .001 for all) (**Figure 2**).

### Changes in Outcomes Over Time

The annual decline in mortality over time did not differ significantly between patients with severe sepsis and all other diagnoses (OR, 0.94 [95% CI, 0.94-0.95] vs 0.94 [95% CI, 0.94-0.94]; *P* = .37) (Figure 2). However, within the severe sepsis population, there was a significant interaction between the decline in risk and patient severity (lowest APACHE III quartile OR, 0.91 [95% CI, 0.88-0.93], highest APACHE III quartile OR, 0.95 [95% CI, 0.93-0.97]), hospital level (rural OR, 0.92 [95% CI, 0.89-0.94], metropolitan OR, 0.95 [95% CI, 0.93-0.97]), hospital admission source (home OR, 0.93 [95% CI, 0.91-0.95], other ICU OR, 0.97 [95% CI, 0.94-1.01]), and hospital location (Western Australia OR, 0.88 [95% CI, 0.85-0.90], Australian Capital Territory OR, 0.98 [95% CI, 0.94-1.01]) (**Table 3**) (all *P* < .001 for interaction).

The annual increase in discharge to home was significantly greater among patients with severe sepsis compared with all nonseptic diagnoses (OR, 1.03 [95% CI, 1.02-1.03] vs 1.01 [95% CI, 1.01-1.01]; *P* < .001). Conversely, the annual increase in patients' discharge to rehabilitation facilities was significantly less in patients with severe sepsis compared with all other diagnoses (OR, 1.08 [95% CI, 1.07-1.09] vs 1.09 [95% CI, 1.09-1.10]; *P* < .001) (eFigure 4 in the Supplement). Sensitivity analysis performed on the 61% of data derived from the 63 hospitals that provided data for each of the 13 years closely replicated these findings (eTable 4 in the Supplement).

We also explored whether there were changes in the time of death (by hospital day) over time (eFigure 5 in the Supplement) and found that the decrease in mortality applied over the full course of hospital stay. Adjusted length of stay for deceased patients showed no trend (*P* = .74) (eFigure 6 in the Supplement).

### Sensitivity Analyses

We analyzed trends in mortality in patients with severe sepsis by stratifying for hospital level, hospital size, and hospital length-of-stay quartiles (eFigure 7 in the Supplement). In addition, we analyzed all outcomes in the subgroup of ICUs that have steadily contributed to the adult ICU patient database

Table 1. Characteristics and Outcomes in Severe Sepsis

| | % (95% CI) | | |
|---|---|---|---|
| | All Patients (N = 101 064) | Without Comorbidities[a] (n = 64 149) | With Comorbidities[a] (n = 36 915) |
| Age, mean (95% CI), y | 63.5 (63.3-63.6) | 62.3 (62.2-62.5) | 65.4 (65.3-65.6) |
| Male sex | 54 (54-54) | 53 (52-53) | 56 (56-57) |
| Sepsis as admission diagnosis | 52 (52-52) | 50 (49-50) | 57 (56-57) |
| Infection as admission diagnosis | 48 (48-48) | 50 (50-51) | 43 (43-44) |
| APACHE III score, mean (95% CI) | 70.9 (70.7-71.1) | 66.6 (66.3-66.8) | 78.4 (78.1-78.7) |
| APACHE III risk of death, median (IQR), % | 21.2 (8.6-46.3) | 16.8 (6.8-37.9) | 30.6 (13.9-58.0) |
| Mechanical ventilation in ICU | 50 (50-50) | 52 (52-52) | 45 (45-46) |
| Length of stay, median (IQR), d | | | |
| ICU | 3.2 (1.6-6.9) | 3.2 (1.6-7.0) | 3.1 (1.6-6.8) |
| Hospital | 13.5 (7.0-25.9) | 13.2 (7.0-25.5) | 13.8 (7.0-26.9) |
| Limitation of treatment | 4 (4-4) | 3 (3-3) | 6 (6-7) |
| ICU mortality | 16 (16-16) | 13 (13-13) | 22 (22-23) |
| Hospital outcome | | | |
| Mortality | 24 (24-24) | 19 (19-19) | 33 (33-34) |
| Discharge to home | 57 (57-57) | 61 (60-61) | 51 (50-51) |
| Discharge to rehabilitation[b] | 7 (7-7) | 8 (8-8) | 6 (6-6) |
| Discharge to other hospital | 11 (11-11) | 12 (12-12) | 10 (9-10) |
| Subgroups | | | |
| Severe sepsis | 49 (49-49) | 50 (50-51) | 48 (47-48) |
| Septic shock | 51 (51-51) | 50 (49-50) | 52 (52-53) |
| Medical admissions | 77 (77-77) | 75 (74-75) | 82 (82-82) |
| Surgical admissions | 23 (23-23) | 25 (25-26) | 18 (18-18) |
| Respiratory failure[c] | 45 (45-45) | 48 (47-48) | 40 (39-40) |
| Acute renal failure[d] | 17 (17-17) | 15 (15-15) | 20 (20-21) |
| APACHE score[e] | | | |
| II <25 | 72 (72-72) | 82 (81-82) | 57 (56-57) |
| II ≥25 | 28 (28-28) | 18 (18-19) | 43 (43-44) |
| III Q1 (<50) | 25 (25-25) | 31 (30-31) | 15 (15-16) |
| III Q2 (50-66) | 25 (25-25) | 26 (25-26) | 24 (23-24) |
| III Q3 (67-87) | 25 (25-25) | 23 (23-23) | 29 (28-29) |
| III Q4 (>87) | 25 (25-25) | 21 (20-21) | 33 (32-33) |
| Age, y | | | |
| ≤44 | 16 (16-16) | 19 (19-19) | 11 (10-11) |
| 45-64 | 30 (30-30) | 28 (28-29) | 32 (32-33) |
| 65-84 | 47 (47-47) | 45 (44-45) | 51 (50-51) |
| ≥85 | 7 (7-7) | 8 (8-8) | 6 (5-6) |
| Sepsis | | | |
| Other than urinary tract origin | 20 (20-20) | 19 (19-20) | 22 (22-23) |
| Urinary tract origin | 7 (7-7) | 7 (7-7) | 6 (5-6) |
| With shock, other than urinary tract | 21 (21-21) | 19 (18-19) | 25 (25-25) |
| Urinary tract origin with shock | 4 (4-4) | 5 (4-5) | 4 (4-4) |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; Q, quartile.

[a] Comorbidity as defined by the APACHE II[23] or APACHE III[24] classification system. Comparisons are made between patients with and without comorbidities ($P < .001$ for all except ICU length of stay where $P = .02$).

[b] Discharge to rehabilitation included discharge to rehabilitation facilities and chronic care facilities such as nursing homes.

[c] Respiratory failure was defined by mechanical ventilation and intubation.

[d] Acute renal failure was defined by highest creatinine ≥3.39 mg/dL or urine output <410 mL/24 h or all of the following: urine output <410 mL/24 h and creatinine ≥1.50 mg/dL and no long-term dialysis. Data for acute renal failure were missing for 103 patients.

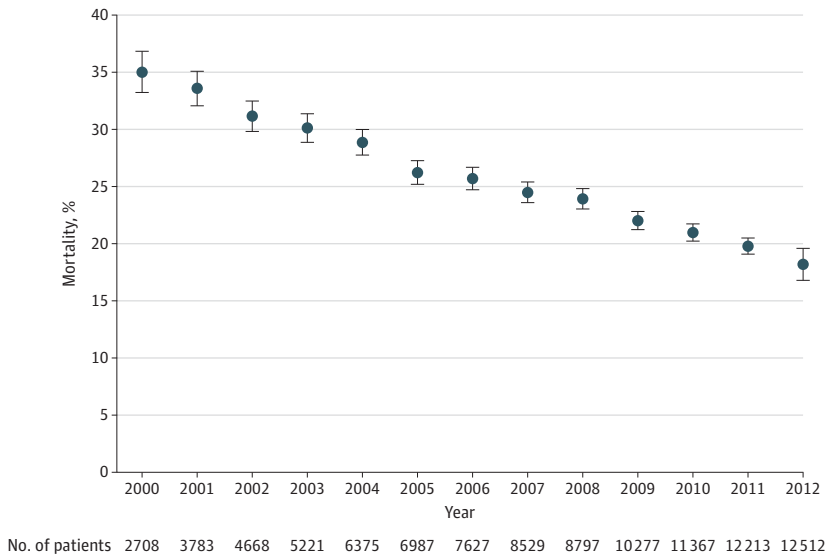
[e] APACHE II and APACHE III scores were missing for 534 patients.

from 2000 to 2012. The findings in these hospitals were the same as in the total cohort (eFigure 8 in the Supplement).

## Discussion

We assessed whether the outcome of severe sepsis with or without shock in Australia and New Zealand has improved from 2000 to 2012. We found that hospital mortality decreased steadily throughout this period. The decrease was systematic and applied to all patients, including multiple subgroups. The decrease in mortality remained statistically significant after adjustments. The same improvement occurred in nonseptic patients, but such patients had lower rates of discharge to home and higher rates of discharge to rehabilitation. These findings were confirmed in sensitivity analyses stratified by hospital level, hospital size, and hospital length of stay and by using only centers that had reported data throughout the study period. In 2012 and in the absence of comorbidities and older age, the mortality rate of severe sepsis or septic shock in Australia and New Zealand was 4.6%.

Figure 1. Mean Annual Mortality in Patients With Severe Sepsis




Error bars indicate 95% CI.

Table 2. Mortality Rate Among Severe Sepsis Patients Overall and Within Subgroups in 2000 and 2012[a]

| | 2000 | | | 2012 | | | Risk Reduction | |
|---|---|---|---|---|---|---|---|---|
| | No. of Events | No. of Patients | Mortality, % (95% CI) | No. of Events | No. of Patients | Mortality, % (95% CI) | Absolute | Relative |
| All patients with severe sepsis | 949 | 2708 | 35.0 (33.2-36.8) | 2300 | 12 512 | 18.4 (17.8-19.0) | 16.7 (14.8-18.6) | 47.5 (44.1-50.8) |
| Without comorbidities[b] | 529 | 1800 | 29.4 (27.2-31.6) | 1136 | 8110 | 14.0 (13.2-14.8) | 15.4 (13.2-17.7) | 52.3 (47.9-56.4) |
| With comorbidities[b] | 420 | 908 | 46.3 (43.0-49.6) | 1164 | 4402 | 26.4 (25.0-27.8) | 19.8 (16.3-23.3) | 42.8 (37.7-47.5) |
| Severe sepsis without shock | 426 | 1411 | 30.2 (27.8-32.6) | 815 | 5755 | 14.2 (13.2-15.2) | 16.0 (13.5-18.6) | 53.1 (48.1-57.6) |
| Septic shock | 523 | 1297 | 40.3 (37.6-43.0) | 1485 | 6757 | 22.0 (21.0-23.0) | 18.3 (15.5-21.2) | 45.5 (41.0-49.7) |
| Medical admissions | 784 | 2052 | 38.2 (36.0-40.4) | 1959 | 9824 | 19.9 (19.1-20.7) | 18.3 (16.0-20.5) | 47.8 (44.1-51.2) |
| Surgical admissions | 165 | 656 | 25.2 (21.9-28.5) | 341 | 2688 | 12.7 (11.5-13.9) | 12.5 (9.0-16.1) | 49.6 (40.5-57.2) |
| Respiratory failure[c] | 652 | 1642 | 39.7 (37.3-42.1) | 1106 | 4603 | 24.0 (22.8-25.2) | 15.7 (13.0-18.4) | 39.5 (34.5-44.1) |
| Acute renal failure[d] | 445 | 805 | 55.3 (51.8-58.8) | 1069 | 3100 | 34.5 (32.7-36.3) | 20.8 (17.0-24.6) | 37.6 (32.5-42.3) |
| APACHE score | | | | | | | | |
| II <25 | 370 | 1679 | 22.0 (20.0-24.0) | 1079 | 9537 | 11.3 (10.7-11.9) | 10.7 (8.7-12.9) | 48.7 (42.9-53.8) |
| II ≥25 | 554 | 942 | 58.8 (55.7-61.9) | 1177 | 2732 | 43.1 (41.3-44.9) | 15.7 (12.0-19.3) | 26.7 (21.5-31.6) |
| III Q1 | 47 | 498 | 9.4 (6.9-11.9) | 77 | 3486 | 2.2 (1.8-2.6) | 7.2 (4.9-10.1) | 76.6 (66.8-83.5) |
| III Q2 | 103 | 544 | 18.9 (15.6-22.2) | 317 | 3254 | 9.7 (8.7-10.7) | 9.2 (5.9-12.8) | 48.5 (37.0-58.0) |
| III Q3 | 215 | 607 | 35.4 (31.7-39.1) | 634 | 3149 | 20.1 (18.7-21.5) | 15.3 (11.3-19.4) | 43.2 (35.4-50.0) |
| III Q4 | 498 | 819 | 60.8 (57.5-64.1) | 1258 | 2591 | 48.6 (46.6-50.6) | 12.3 (8.4-16.1) | 20.2 (14.6-25.4) |
| Age, y | | | | | | | | |
| ≤44 | 98 | 443 | 22.1 (18.2-26.0) | 130 | 1778 | 7.3 (6.1-8.5) | 14.8 (11.0-19.1) | 66.9 (58.0-74.0) |
| 45-64 | 226 | 742 | 30.5 (27.2-33.8) | 524 | 3660 | 14.3 (13.1-15.5) | 16.1 (12.7-19.7) | 53.0 (46.2-58.9) |
| 65-84 | 537 | 1326 | 40.5 (38.0-43.0) | 1260 | 5806 | 21.7 (20.7-22.7) | 18.8 (16.0-21.7) | 46.4 (41.9-50.6) |
| ≥85 | 88 | 197 | 44.7 (37.6-51.8) | 386 | 1268 | 30.4 (27.9-32.9) | 14.2 (7.0-21.6) | 31.9 (18.7-42.9) |
| Sepsis | | | | | | | | |
| Other than urinary tract origin | 131 | 412 | 31.8 (27.3-36.3) | 470 | 2770 | 17.0 (15.6-18.4) | 14.8 (10.3-19.7) | 46.6 (37.1-54.7) |
| Urinary tract origin | 26 | 113 | 23.0 (15.2-30.8) | 66 | 982 | 6.7 (5.1-8.3) | 16.3 (9.3-25.0) | 70.8 (56.0-80.6) |
| With shock, other than urinary tract | 365 | 747 | 48.9 (45.4-52.4) | 703 | 2419 | 29.1 (27.3-30.9) | 19.8 (15.8-23.8) | 40.5 (34.5-46.0) |
| Urinary tract origin with shock | 26 | 93 | 28.0 (18.8-37.2) | 104 | 686 | 15.2 (12.5-17.9) | 12.8 (4.2-23.0) | 45.8 (21.4-62.6) |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; Q, quartile.

[a] The risk reduction from 2000 to 2012 was statistically significant for all categories: $P < .001$.

[b] Comorbidity as defined by the APACHE II[23] or APACHE III[24] classification system.

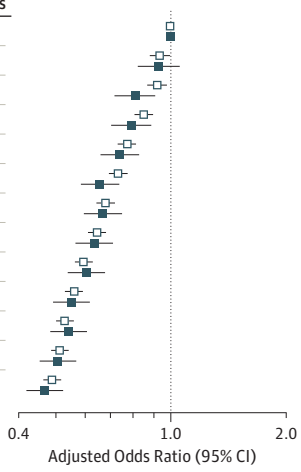
[c] Respiratory failure was defined by mechanical ventilation and intubation.

[d] Acute renal failure was defined by highest creatinine ≥3.39 mg/dL or urine output <410 mL/24 h or all of the following: urine output <410 mL/24 h and creatinine ≥1.50 mg/dL and no long-term dialysis.

Figure 2. Adjusted Annual Odds for the Change in Hospital Outcomes Reported as Odds Ratios Referenced Against the Year 2000

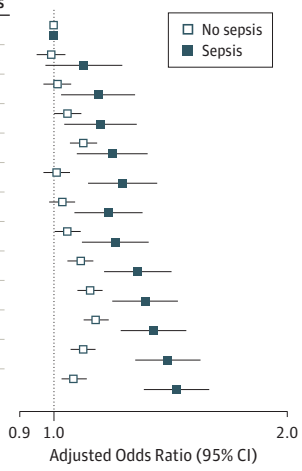
A Mortality

| Year of ICU Admission | No. of Patients | | No. of Events | |
|---|---|---|---|---|
| | Sepsis | No Sepsis | Sepsis | No Sepsis |
| 2000 | 2708 | 35014 | 949 | 4807 |
| 2001 | 3783 | 45000 | 1271 | 5855 |
| 2002 | 4668 | 51972 | 1455 | 6484 |
| 2003 | 5221 | 58393 | 1573 | 6996 |
| 2004 | 6375 | 65292 | 1841 | 7383 |
| 2005 | 6987 | 72220 | 1833 | 7825 |
| 2006 | 7627 | 75926 | 1961 | 7765 |
| 2007 | 8529 | 78297 | 2090 | 7844 |
| 2008 | 8797 | 77379 | 2106 | 7541 |
| 2009 | 10277 | 84842 | 2264 | 7943 |
| 2010 | 11367 | 93385 | 2386 | 8302 |
| 2011 | 12213 | 98045 | 2418 | 8535 |
| 2012 | 12512 | 100286 | 2300 | 8010 |



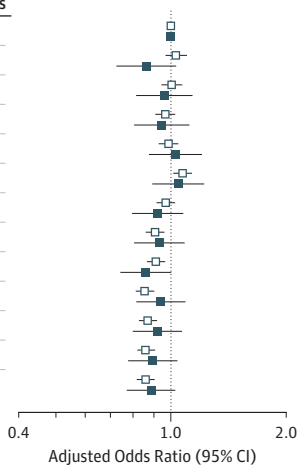

B Discharged Home

| No. of Events | |
|---|---|
| Sepsis | No Sepsis |
| 1371 | 26648 |
| 1960 | 34223 |
| 2486 | 39716 |
| 2829 | 44674 |
| 3462 | 49559 |
| 3938 | 54588 |
| 4238 | 57172 |
| 4763 | 58521 |
| 5003 | 57499 |
| 5955 | 62986 |
| 6743 | 69575 |
| 7418 | 72459 |
| 7699 | 74443 |



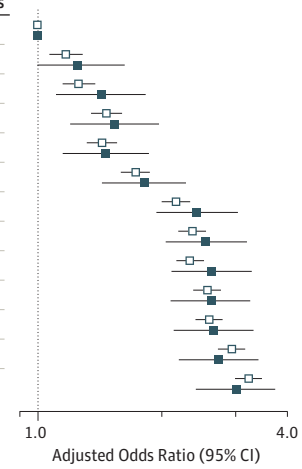

C Discharged to Another Hospital

| Year of ICU Admission | No. of Patients | | No. of Events | |
|---|---|---|---|---|
| | Sepsis | No Sepsis | Sepsis | No Sepsis |
| 2000 | 2708 | 35014 | 278 | 2425 |
| 2001 | 3783 | 45000 | 374 | 3260 |
| 2002 | 4668 | 51972 | 479 | 3959 |
| 2003 | 5221 | 58393 | 537 | 4293 |
| 2004 | 6375 | 65292 | 706 | 5151 |
| 2005 | 6987 | 72220 | 800 | 6326 |
| 2006 | 7627 | 75926 | 841 | 6356 |
| 2007 | 8529 | 78297 | 1015 | 6731 |
| 2008 | 8797 | 77379 | 964 | 6940 |
| 2009 | 10277 | 84842 | 1236 | 7319 |
| 2010 | 11367 | 93385 | 1327 | 8186 |
| 2011 | 12213 | 98045 | 1401 | 8642 |
| 2012 | 12512 | 100286 | 1443 | 8733 |




D Discharged to Rehabilitation

| No. of Events | |
|---|---|
| Sepsis | No Sepsis |
| 110 | 1134 |
| 178 | 1662 |
| 248 | 1813 |
| 282 | 2430 |
| 366 | 3199 |
| 416 | 3481 |
| 587 | 4633 |
| 661 | 5201 |
| 724 | 5399 |
| 822 | 6594 |
| 911 | 7322 |
| 976 | 8409 |
| 1070 | 9100 |




When considered as a continuous variable, there was no difference between patients with severe sepsis or septic shock and other patients in the database for the decline in mortality over time (odds ratio [OR], 0.94 [95% CI, 0.94-0.95] vs 0.94 [95% CI, 0.94-0.94]; $P = .37$), whereas significant differences were observed in the change over time for discharge to home (OR, 1.03 [95% CI, 1.02-1.03] vs 1.01 [95% CI, 1.01-1.01]; $P < .001$) and discharge to rehabilitation facilities (OR, 1.08 [95% CI, 1.07-1.09] vs 1.09 [95% CI, 1.09-1.10]; $P < .001$). Discharge to rehabilitation included discharge to rehabilitation facilities and chronic care facilities such as nursing homes. ICU indicates intensive care unit.

## Relationship to Previous Studies

The prevalence of severe sepsis on admission in the overall ICU population was 9.7%, almost identical to a previous detailed prospective study in Australia and New Zealand ICUs.[27] In addition, a Danish study comparing identification of septic shock from a national clinical database and screening of individual patient data found high accuracy in the diagnosis of septic shock,[28] supporting the likely robustness of our methodology. The year 2000 mortality was also the same as in the PROWESS study placebo group, supporting the external validity of our findings.[3] Detailed prospective observational data from Australia and New Zealand in 1999 reported a hospital mortality of 37.5% and 28-day mortality of 32.4%,[27] further confirming of the likely validity of our baseline year 2000 estimate of 35.0% mortality and suggesting that hospital mortality and 28-day mortality may be similar in Australia and New Zealand.

We observed a systematic continuous trend toward lower mortality in severe sepsis. Similar decreases in mortality over time have been reported in other retrospective studies.[1,29-31] The Surviving Sepsis Campaign has reported decreasing mortality rates in severe sepsis.[32] In the United States, the decrease in severe sepsis mortality varied from 1.1% to 1.9% annually during a 6-year period in all hospital patients[1] and a relative decrease by 51% during a 24-year period in ICU patients.[31]

Variations in the definition of severe sepsis can explain differences in mortality rates among septic patients.[25,33,34] Large RCTs with mortality rates of 25.4% to 46.9% in the placebo group used the ACCP/SCCM criteria to define severe sepsis.[11,12,14,35,36] How-

Table 3. Odds Ratios for the Annual Change in Risk for Hospital Outcomes for Patients With Severe Sepsis[a]

| | No. of Patients | OR (95%CI) | | | |
|---|---|---|---|---|---|
| | | Mortality | Discharge to Home | Discharge to Other Hospital | Discharge to Rehabilitation |
| Overall change, y | 101 064 | 0.94 (0.94-0.95) | 1.03 (1.02-1.03) | 1.01 (1.00-1.01) | 1.06 (1.05-1.07) |
| APACHE III score | | | | | |
| Q1 (<50) | 25 055 | 0.91 (0.88-0.93) | 1.03 (1.01-1.05) | 0.99 (0.96-1.02) | 1.05 (1.01-1.09) |
| Q2 (50-66) | 24 979 | 0.93 (0.91-0.96) | 1.03 (1.01-1.05) | 0.99 (0.97-1.02) | 1.06 (1.02-1.10) |
| Q3 (67-87) | 25 620 | 0.94 (0.92-0.96) | 1.03 (1.01-1.04) | 1.01 (0.98-1.04) | 1.07 (1.03-1.11) |
| Q4 (>87) | 24 876 | 0.95 (0.93-0.97) | 1.03 (1.01-1.05) | 1.03 (1.00-1.06) | 1.08 (1.04-1.12) |
| ICU type | | | | | |
| ICU | 80 164 | 0.93 (0.91-0.95) | 1.03 (1.01-1.05) | 1.01 (0.98-1.04) | 1.05 (1.02-1.09) |
| High-dependency unit | 14 809 | 0.94 (0.91-0.96) | 1.02 (1.00-1.04) | 1.01 (0.98-1.04) | 1.01 (0.97-1.06) |
| Hospital level | | | | | |
| Rural | 17 419 | 0.92 (0.89-0.94) | 1.04 (1.02-1.06) | 1.01 (0.99-1.04) | 1.06 (1.01-1.10) |
| Metropolitan | 25 754 | 0.95 (0.93-0.97) | 1.01 (0.99-1.03) | 1.03 (1.00-1.05) | 1.04 (1.00-1.08) |
| Tertiary | 46 883 | 0.93 (0.91-0.95) | 1.03 (1.01-1.05) | 1.01 (0.98-1.04) | 1.08 (1.05-1.12) |
| Private | 11 008 | 0.94 (0.92-0.96) | 1.05 (1.03-1.07) | 0.94 (0.91-0.97) | 1.05 (1.02-1.09) |
| Hospital admission source | | | | | |
| Home | 67 157 | 0.93 (0.91-0.95) | 1.03 (1.01-1.05) | 1.01 (0.98-1.03) | 1.06 (1.02-1.09) |
| Other hospital | 23 769 | 0.93 (0.91-0.95) | 1.03 (1.01-1.05) | 1.00 (0.98-1.03) | 1.04 (1.00-1.08) |
| Chronic care | 2289 | 0.94 (0.90-0.97) | 0.99 (0.96-1.03) | 0.96 (0.92-1.01) | 1.09 (1.04-1.14) |
| Other ICU | 1797 | 0.97 (0.94-1.01) | 1.00 (0.96-1.03) | 0.98 (0.94-1.02) | 1.17 (1.09-1.25) |
| Unknown | 6052 | 0.93 (0.90-0.96) | 0.98 (0.95-1.00) | 1.04 (1.00-1.08) | 1.21 (1.15-1.27) |
| State or country | | | | | |
| Australian Capital Territory | 2613 | 0.98 (0.94-1.01) | 0.99 (0.97-1.02) | 1.03 (0.99-1.07) | 1.03 (0.96-1.10) |
| New South Wales | 31 782 | 0.93 (0.91-0.95) | 1.04 (1.02-1.06) | 1.00 (0.97-1.02) | 1.07 (1.04-1.11) |
| Northern Territory | 3375 | 0.94 (0.91-0.97) | 1.03 (1.01-1.06) | 1.03 (0.99-1.07) | 0.82 (0.75-0.90) |
| Queensland | 18 065 | 0.93 (0.91-0.95) | 1.02 (1.00-1.04) | 0.99 (0.97-1.02) | 1.13 (1.10-1.17) |
| South Australia | 9620 | 0.94 (0.91-0.96) | 1.06 (1.04-1.08) | 1.01 (0.98-1.04) | 0.97 (0.94-1.01) |
| Tasmania | 2275 | 0.94 (0.91-0.97) | 1.06 (1.03-1.09) | 0.93 (0.89-0.97) | 1.10 (1.02-1.17) |
| Victoria | 22 891 | 0.93 (0.92-0.95) | 1.01 (0.99-1.02) | 1.01 (0.98-1.03) | 1.07 (1.04-1.11) |
| Western Australia | 3562 | 0.88 (0.85-0.90) | 1.03 (1.00-1.05) | 1.00 (0.97-1.04) | 1.18 (1.12-1.23) |
| New Zealand | 6881 | 0.93 (0.91-0.96) | 1.03 (1.00-1.05) | 1.07 (1.03-1.11) | 0.99 (0.95-1.03) |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; OR, odds ratio; Q, quartile.

[a] Change in risk was statistically significant for all categories: $P < .001$.

ever, these studies had additional criteria to include patients with greater illness severity, which explains some of the difference between these studies and the mortality rate in our study. With the more stringent criteria for disease severity than those used in our study, the anticipated mortalities for these studies were 40%,[11] 60%,[12] 50%,[14] and 45%,[35] whereas the respective observed mortalities were 25.4%, 39.3%, 42.9% to 45.8%, and 43%. In our study, we applied the same criteria during the entire observation period from 2000 to 2012 to study time-related changes in mortality. The decrease in mortality was consistent across all patient subgroups including analysis by different levels of disease severity and by adjustments for confounders.

In the Surviving Sepsis Campaign, there were significantly different crude mortality rates, 41.1% in Europe vs 28.3% in the United States. However, when adjusted for disease severity, the difference disappeared.[37] Within the United States, mortality has been 17.9%[30] or 39%[38] when the same criteria for severe sepsis were applied to hospitalized patients with data retrieved from different databases. Our study reports data from 1 single database that, by 2012, covered more than 90% of all ICU admissions in Australia and New Zealand. Our findings remained after adjustments for illness severity, risk of developing sepsis, center effect, and hospital size effect; after sensitivity analysis; and after excluding the effect of patients discharged to other hospitals or to rehabilitation centers.

## Implications of Study Findings

Our study provides evidence that sepsis-related mortality has steadily decreased over time even after adjustments for illness severity, center effect, regional effects, hospital size, risk of being septic, and other key variables. It is unclear whether any improvements in diagnostic procedures, earlier and broader-spectrum antibiotic treatment, or more aggressive supportive therapy according to severity of the disease[32,39] contributed to this change. The observation that an equivalent improvement occurred in nonseptic patients supports the view that overall changes in ICU practice rather than in the management of sepsis explain most of our findings. These changes in outcome remained after multiple adjustments for confounders, including illness severity, and even after taking into ac-

count changes in discharge destinations. This makes it unlikely that the decrease in mortality is dependent only on less sick patients being admitted to ICU or on patients being discharged to other hospitals or to rehabilitation.

Comorbidities were present in 35% of patients. This implies that, if such a significant proportion of sepsis patients were excluded from RCTs, there would be a risk of selection bias and recruitment failure. If such patients are excluded, the mortality figures used for power calculations should be based on the lower mortality rate seen in comorbidity-free patients (14.0% in 2012). Young septic patients without comorbidities represent a group of patients where the mortality attributable to sepsis can be assessed with fewer confounders.[40] The mortality of severe sepsis in these patients was 4.6% in 2012. Given such low mortality rates, long-term morbidity and quality of life will likely become the focus of future trials.[41]

Although no single explanation can be offered for our findings, they challenge the view that little progress has been made in the management of severe sepsis. They also suggest that outcomes for severe sepsis should be interpreted according to the year of data collection and that, on average, a yearly 1% improvement in crude mortality can be expected. Accordingly, RCTs in this field that last several years should consider this effect when estimating statistical power. Mortality in severe sepsis or septic shock appears lower than in published figures used for calculations of trial sample size.[6,9-15] This overestimation of mortality may lead to underpowered studies and to potentially useful therapies being abandoned because of lack of evidence.[18] Finally, our findings provide a point of reference for current and evolving hospital mortality rates in septic patients overall and in specific subgroups of septic patients.

### Strengths and Weaknesses

To our knowledge, our study is the only investigation of changes in mortality in septic ICU patients over an entire decade with adjustment for APACHE III risk of death and for multiple other relevant covariates and with identification and consistent use of the same full criteria for severe sepsis and septic shock on the day of admission. Second, we retrieved the data from a database that, by 2012, included more than 90% of all ICU admission in the binational area of Australia and New Zealand. The data were collected prospectively for routine quality surveillance purposes. Such data, therefore, are unlikely to be biased or affected by changing diagnostic criteria. Third, the size of the study cohort enabled robust annual analysis of mortality rates. Fourth, the findings were consistent in subgroups and consistent with existing literature. Finally, the incidence of severe sepsis in ICU patients was identical to that reported in the previous prospective study of the same ICUs.

Our findings are limited by the fact that the diagnosis of severe sepsis only applied to patient characteristic during the first 24 hours in ICU. Thus, patients who developed severe sepsis later while in the ICU were not analyzed. The accuracy of severe sepsis diagnosis was not monitored, but the data were collected by trained collectors and we used physiological coding for systemic inflammatory response syndrome and organ failure, which are less subject to coding artifact. We also accounted for the APACHE admission diagnoses of sepsis as well as APACHE admission diagnoses for infection to ensure that diagnostic coding changes would not affect the capture of all severe sepsis.[42] In addition, the diagnostic criteria for severe sepsis were kept constant throughout the study, enabling us to detect changes in mortality over time in an unbiased way. Finally, we can only report hospital mortality, which may be higher than 28-day mortality[8,27,43] but is likely lower than 90-day mortality[10,14] and can be used as a surrogate for 30-day mortality.[44,45]

## Conclusions

In critically ill patients in Australia and New Zealand with severe sepsis with or without shock, there was a decrease in mortality from 2000 to 2012. These findings were accompanied by changes in the patterns of discharge to home, rehabilitation, and other hospitals.

ARTICLE INFORMATION

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**Author Contributions:** Dr Bailey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Kaukonen, Bellomo.
*Acquisition of data:* Bailey, Pilcher.
*Analysis and interpretation of data:* Kaukonen, Bailey, Suzuki, Pilcher, Bellomo.
*Drafting of the manuscript:* Kaukonen, Bailey, Pilcher, Bellomo.
*Critical revision of the manuscript for important intellectual content:* Kaukonen, Bailey, Suzuki, Pilcher, Bellomo.
*Statistical analysis:* Bailey, Pilcher.
*Administrative, technical, or material support:* Kaukonen.
*Study supervision:* Bellomo.

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