

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-Majja 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.

JAMA. doi:10.1001/jama.2014.2637
Published online March 18, 2014.

← Editorial

+ Supplemental content at
jama.com

Author Affiliations: Australian and New Zealand Intensive Care Research Centre (ANZIC RC), Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia (Kaukonen, Bailey, Pilcher, Bellomo); Critical Care Research Group, Intensive Care Unit, Helsinki University Central Hospital, Helsinki, Finland (Kaukonen); Intensive Care Unit, Austin Health, Heidelberg, Australia (Suzuki, Bellomo); ANZICS Centre for Outcome and Resource Evaluation CORE, Melbourne, Australia (Pilcher); Department of Intensive Care, The Alfred Hospital, Melbourne, Australia (Pilcher).

Corresponding Author: Rinaldo Bellomo, MD, PhD, Department of Intensive Care, Austin Health, Heidelberg, Victoria 3084, Australia (rinaldo.bellomo@austin.org.au).

Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, JAMA (angusdc@upmc.edu).

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 hydrocortisone⁵ showed promise. However, later pivotal RCTs⁶⁻¹⁵ 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 eritoran¹⁵ 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 database²⁰ 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 Statistics²¹ 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) II²³ or APACHE III²⁴ 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 presum-

ably 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, χ^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 II²³ or APACHE III²⁴ 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.

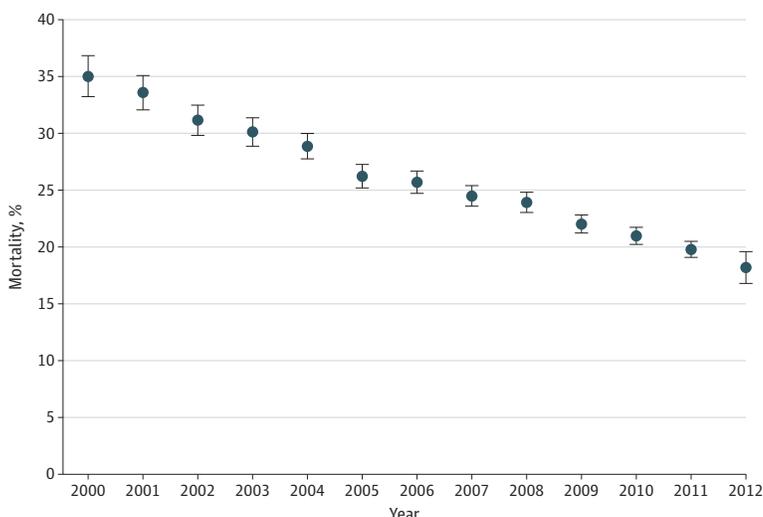
from 2000 to 2012. The findings in these hospitals were the same as in the total cohort (eFigure 8 in the Supplement).

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



No. of patients 2708 3783 4668 5221 6375 6987 7627 8529 8797 10277 11367 12213 12512

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.

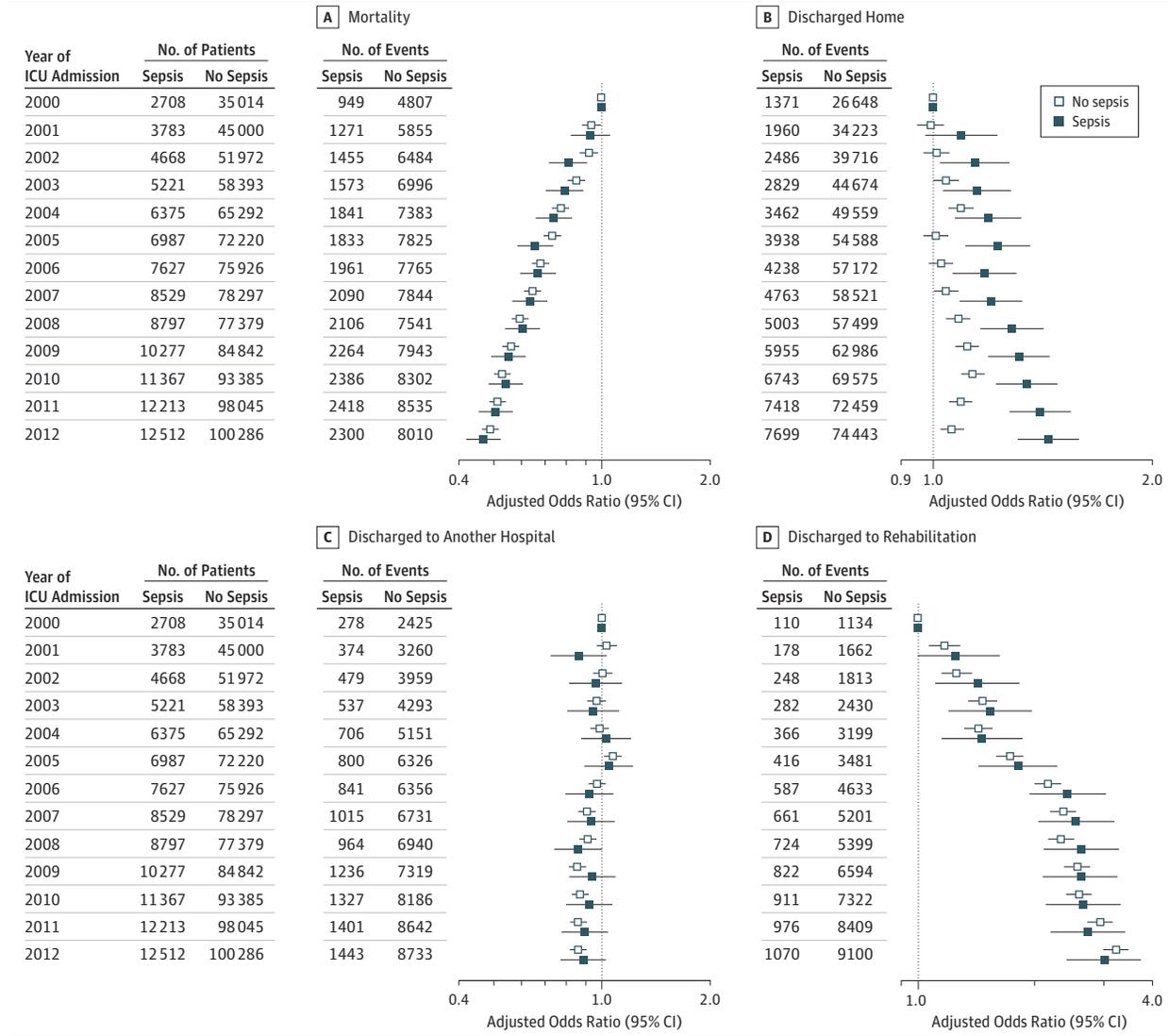
^c Respiratory failure was defined by mechanical ventilation and intubation.

^a The risk reduction from 2000 to 2012 was statistically significant for all categories: *P* < .001.

^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.

^b Comorbidity as defined by the APACHE II²³ or APACHE III²⁴ classification system.

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



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 patients¹ 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

Published Online: March 18, 2014.
doi:10.1001/jama.2014.2637.

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.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for

Disclosure of Potential Conflicts of Interest. Dr Kaukonen reported having received a grant for clinical research career from the Academy of Finland. Dr Bellomo reported having received personal fees and nonfinancial support from Gambro, grants and personal fees from Baxter, and personal fees from Philips and Braun. No other disclosures were reported.

REFERENCES

1. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med*. 2013;41(5):1167-1174.
2. Brun-Buisson C, Meshaka P, Pinton P, Vallet B; EPISEPSIS Study Group. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med*. 2004;30(4):580-588.
3. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10):699-709.
4. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
5. Annane D, S ebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862-871.
6. Warren BL, Eid A, Singer P, et al; KyberSept Trial Study Group. Caring for the critically ill patient: high-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA*. 2001;286(15):1869-1878.
7. Abraham E, Reinhart K, Opal S, et al; OPTIMIST Trial Study Group. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA*. 2003;290(2):238-247.

8. Abraham E, Laterre P-F, Garg R, et al; Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med*. 2005;353(13):1332-1341.
9. Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock: a randomised trial. *N Engl J Med*. 2012;366(22):2055-2064.
10. Annane D, Vignon P, Renault A, et al; CATS Study Group. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370(9588):676-684.
11. Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-139.
12. Russell JA, Walley KR, Singer J, et al; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887.
13. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
14. Annane D, Cariou A, Maxime V, et al; COIITSS Study Investigators. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA*. 2010;303(4):341-348.
15. Opal SM, Laterre P-F, Francois B, et al; ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. *JAMA*. 2013;309(11):1154-1162.
16. Peake SL, Bailey M, Bellomo R, et al; ARISE Investigators, for the Australian and New Zealand Intensive Care Society Clinical Trials Group. Australasian resuscitation of sepsis evaluation (ARISE): a multi-centre, prospective, inception cohort study. *Resuscitation*. 2009;80(7):811-818.
17. Ho BCH, Bellomo R, McGain F, et al. The incidence and outcome of septic shock patients in the absence of early-goal directed therapy. *Crit Care*. 2006;10(3):R80.
18. Aberegg SK, Richards DR, O'Brien JM. Delta inflation: a bias in the design of randomized controlled trials in critical care medicine. *Crit Care*. 2010;14(2):R77.
19. Bellomo R, Lipcsey M. Xigris 2011: deja vu all over again? *Crit Care Resusc*. 2011;13(4):211-212.
20. Stow PJ, Hart GK, Higglet T, et al; ANZICS Database Management Committee. Development and implementation of a high-quality clinical database: the Australian and New Zealand Intensive Care Society Adult Patient Database. *J Crit Care*. 2006;21(2):133-141.
21. 3101.O: Australian Demographic Statistics, Dec 2012. Australian Bureau of Statistics. <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Dec2012?OpenDocument>. Accessed August 1, 2013.
22. QuickStats About New Zealand's Population and Dwellings. Statistics New Zealand. <http://www.stats.govt.nz/Census/2006CensusHomePage/QuickStats/quickstats-about-a-subject/nzs-population-and-dwellings.aspx>. Accessed August 1, 2013.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.
24. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100(6):1619-1636.
25. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20(6):864-874.
26. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure: on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
27. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med*. 2004;30(4):589-596.
28. Grønlykke L, Brandstrup SL, Perner A. Data from clinical database on septic shock are valid. *Dan Med J*. 2012;59(10):A4522.
29. Banta JE, Joshi KP, Beeson L, Nguyen HB. Patient and hospital characteristics associated with inpatient severe sepsis mortality in California, 2005-2010. *Crit Care Med*. 2012;40(11):2960-2966.
30. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.
31. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit Care*. 2013;17(2):R81.
32. Levy MM, Dellinger RP, Townsend SR, et al; Surviving Sepsis Campaign. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med*. 2010;38(2):367-374.
33. Vincent J-L, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. *Lancet*. 2013;381(9868):774-775.
34. Zhao H, Heard SO, Mullen MT, et al. An evaluation of the diagnostic accuracy of the 1991 American College of Chest Physicians/Society of Critical Care Medicine and the 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society sepsis definition. *Crit Care Med*. 2012;40(6):1700-1706.
35. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.
36. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkley AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. *Crit Care Med*. 2014;42(3):625-631.
37. Levy MM, Artigas A, Phillips GS, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. *Lancet Infect Dis*. 2012;12(12):919-924.
38. Kumar G, Kumar N, Taneja A, et al; Milwaukee Initiative in Critical Care Outcomes Research Group of Investigators. Nationwide trends of severe sepsis in the 21st century (2000-2007). *Chest*. 2011;140(5):1223-1231.
39. Miller RR III, Dong L, Nelson NC, et al; Intermountain Healthcare Intensive Medicine Clinical Program. Multicenter implementation of a severe sepsis and septic shock treatment bundle. *Am J Respir Crit Care Med*. 2013;188(1):77-82.
40. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med*. 2006;34(1):15-21.
41. Webb SA, Litton E, Barned KL, Crozier TM. Treatment goals: health care improvement through setting and measuring patient-centred outcomes. *Crit Care Resusc*. 2013;15(2):143-146.
42. Lindenaier PK, Lagu T, Shieh MS, Pekow PS, Rothberg MB. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003-2009. *JAMA*. 2012;307(13):1405-1413.
43. Poukkanen M, Vaara ST, Pettilä V, et al; FINNAKI study group. Acute kidney injury in patients with severe sepsis in Finnish intensive care units. *Acta Anaesthesiol Scand*. 2013;57(7):863-872.
44. Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901-1911.
45. Graham PL, Cook DA. Prediction of risk of death using 30-day outcome: a practical end point for quality auditing in intensive care. *Chest*. 2004;125(4):1458-1466.