Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007

Tara Lagu, MD, MPH; Michael B. Rothberg, MD, MPH; Meng-Shiou Shieh, PhD; Penelope S. Pekow, PhD; Jay S. Steingrub, MD; Peter K. Lindenauer, MD, MSc

Objectives: **To assess trends in number of hospitalizations, outcomes, and costs of severe sepsis in the United States.**

Design: **Temporal trends study using the Nationwide Inpatient Sample.**

Patients: **Adult patients with severe sepsis (defined as a diagnosis of sepsis and organ dysfunction) diagnosed between 2003 and 2007.**

Measurements and Main Results: **We determined the weighted frequency of patients hospitalized with severe sepsis. We calculated age- and sex-adjusted population-based mortality rates for severe sepsis per 100,000 population and also used logistic regression to adjust in-hospital mortality rates for patient characteristics. We calculated inflation-adjusted costs using hospital-specific cost-to-charge ratios. We identified a rapid steady increase in the number of cases of severe sepsis, from 415,280 in 2003 to 711,736 in 2007 (a 71% increase). The total hospital costs for all patients with severe sepsis increased from $15.4 billion in 2003 to $24.3 billion in 2007 (57% increase). The proportion of patients with severe sepsis and only a single organ dysfunction decreased from 51% in 2003 to 45% in 2007 ($p < .001$), whereas the proportion of patients with three or four or more organ dysfunctions increased 1.19-fold and 1.51-fold, respectively ($p < .001$). During the same time period, we observed 2% decrease per year in hospital mortality for patients with severe sepsis ($p < .001$), as well as a slight decrease in the length of stay (9.9 days to 9.2 days; $p < .001$) and a significant decrease in the geometric mean cost per case of severe sepsis ($20,210 per case in 2003 and $19,330 in 2007; $p = .025$).**

Conclusions: **The increase in the number of hospitalizations for severe sepsis coupled with declining in-hospital mortality and declining geometric mean cost per case may reflect improvements in care or increases in discharges to skilled nursing facilities; however, these findings more likely represent changes in documentation and hospital coding practices that could bias efforts to conduct national surveillance. (Crit Care Med 2012; 40:754–761)**

Key Words: case fatality; costs; mortality; sepsis; trends analysis

Severe sepsis, defined as a clinical syndrome of infection plus organ dysfunction (1), is the leading cause of in-hospital death in the United States. It was estimated that there were 750,000 annual cases of severe sepsis in the United States in 1995, with a total cost of $17 billion (2). Some have suggested that this figure may have been an overestimate of the number of severe sepsis cases in the United States in 1995, in part because of the methods used to define severe sepsis included many different infectious processes (3). A different approach identified fewer severe sepsis cases per year but a rapid increase in number of hospitalizations, from 168,239 cases in 1993 to 391,544 cases in 2003 (4, 5). Intensivists and policymakers therefore have predicted severe shortages of critical care resources, including physicians, nurses, and intensive care unit beds (6–16).

In the years since these studies were published, new International Classification of Diseases, Ninth Revision, Clinical Modification codes were introduced that are specific to severe sepsis. Surveillance of numbers of cases of severe sepsis may be affected by the introduction of these new codes. Furthermore, the introduction of new technologies (such as electronic systems that calculate glomerular filtration rate) may have led to changes in documentation and coding of organ dysfunction. Despite these changes and concern for rapid growth in hospitalizations, there have been no recent efforts to assess the clinical and economic impacts of sepsis or severe sepsis. We therefore aimed to examine changes in the incidence, number of hospitalizations, outcomes, and costs of hospitalization for severe and nonsevere sepsis over the period 2003 to 2007, with a focus on changes in occurrence of specific organ dysfunctions, the impact of changes in coding and documentation, and changes in costs of care over time.

MATERIALS AND METHODS

Data Sources. We conducted a temporal trends study from 2003 to 2007 using data from the Nationwide Inpatient Sample (NIS), the largest all-payer, publicly available, national hospital database. NIS contains a 20% stratified sample of all short-term, nonfederal, nonrehabilitation hospitals, representing between five million and eight million discharges per year. It was developed as part of the Healthcare Cost and Utilization Project, which is sponsored by the Agency for Healthcare Research and Quality (17). Hospitals are

From the Center for Quality of Care Research (TL, MBR, MS, PSP, JSS, PKL), Baystate Medical Center, Springfield, MA; Division of General Medicine and Geriatrics (TL, MBR), Baystate Medical Center, Springfield, MA; Department of Medicine (TL, MBR, JSS, PKL), Tufts University School of Medicine, Boston, MA; School of Public Health and Health Sciences (PSP), University of Massachusetts-Amherst, MA; Division of Critical Care Medicine (JSS), Baystate Medical Center, Springfield, MA.

Supported, in part, by funding from the Division of Critical Care and the Center for Quality of Care Research at Baystate Medical Center.

Dr. Rothberg is the recipient of a clinical scientist development award from the Doris Duke Charitable Foundation. Dr. Steingrub has received research grant support and participates in the lecture bureau of Eli Lilly & Company. The remaining authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: lagutc@gmail.com

DOI: 10.1097/CCM.0b013e318232db65

Table 1. International Classification of Diseases, Ninth Revision, Clinical Modification codes for sepsis

038 Septicemia
- 038.0 Streptococcal septicemia
- 038.1 Staphylococcal septicemia
- 038.2 Pneumococcal septicemia [Streptococcus pneumoniae septicemia]
- 038.3 Septicemia due to anaerobes
  - Septicemia due to bacteroides
  - Excludes: gas gangrene (040.0)
    - due to anaerobic streptococci (038.0)
- 038.4 Septicemia due to other gram-negative organisms
  - 038.40 Gram-negative organism, unspecified
    - Gram-negative septicemia not otherwise specified
  - 038.41 *Hemophilus influenzae* [*H. influenzae*]
  - 038.42 *Escherichia coli* [*E. coli*]
  - 038.43 Pseudomonas
  - 038.44 Serratia
  - 038.49 Other
- 038.8 Other specified septicemias
  - Excludes: septicemia (due to):
    - anthrax (022.3)
    - gonococcal (098.89)
    - herpetic (054.5)
    - meningococcal (036.2)
    - septicemic plague (020.2)
- 038.9 Unspecified septicemia
  - Septicemia not otherwise specified
  - Excludes: bacteremia not otherwise specified (790.7)
- 995.92 Severe sepsis
- 995.91 Inflammatory response due to infection without organ dysfunction

003.1 Salmonella septicemia
020.2 Septicemic plague
022.3 Anthrax septicemia
036.2 Meningococcal septicemia
036.3 Waterhouse-Friderichsen syndrome
054.5 Herpetic septicemia
098.89 Gonococcemia
112.5 Systemic candidiasis
785.52 Septic shock

Table 2. International Classification of Diseases, Ninth Revision, Clinical Modification codes for organ dysfunction

Respiratory	
518.5	Pulmonary insufficiency following trauma, shock, or surgery
518.81	Acute respiratory failure
518.82	Acute respiratory distress syndrome
518.84	Acute and chronic respiratory failure
518.85	Acute respiratory distress syndrome following trauma, shock, or surgery
786.09	Respiratory abnormality, not otherwise specified
799.1	Respiratory arrest
967.0	Continuous mechanical ventilation-unspecified duration
967.1	Continuous mechanical ventilation <96 hrs
967.2	Continuous mechanical ventilation 96+ hrs
Cardiovascular	
427.5	Cardiac arrest
458.0	Hypotension (458.2, 458.8, 458.9)
785.50	Shock not otherwise specified
785.51	Shock, cardiogenic
785.52	Septic shock
785.59	Shock without trauma
796.3	Low blood pressure, nonspecific
Renal	
580	Acute glomerulonephritis (580.4, 580.0, 580.81, 580.89, 580.9)
584	Acute renal failure (includes 584.5, 584.6,584.7,584.8, 584.9)
Hepatic	
570	Acute necrosis of liver
572.2	Hepatic coma
573.3	Hepatitis, unspecified; not due to virus, congestion, infarction
Hematologic	
286.6	Purpura fulminans
286.9	Coagulopathy
287.3	Primary thrombocytopenia
287.4	Secondary thrombocytopenia
287.5	Thrombocytopenia, unspecified
Metabolic	
276.2	Acidosis, metabolic or lactic
Neurologic	
293.0	Acute delirium
293.1	Subacute delirium
293.9	Transient organic mental disorder, not otherwise specified
348.1	Anoxic brain injury
348.3	Encephalopathy-unspecified
348.31	Septic encephalopathy
348.39	Other encephalopathy
780.01	Coma
780.09	Stupor
Other	
995.92	Severe sepsis (sepsis with acute organ dysfunction)

sampled according to characteristics, such as geographic region, ownership, location (urban/rural), and number of beds. The NIS has been used to study trends in many different populations, including studies of critically ill patients, and has been validated against the National Hospital Discharge Survey (5, 18–20). All discharges from sampled hospitals are included in the database. We obtained national census data from the U.S. Census to calculate population rates. The Baystate Medical Center Institutional Review Board examined the study protocol and, because of the deidentified nature of NIS, deemed this study "not human subjects research," which therefore was exempt from further review (the requirement for informed consent was also waived).

Subjects. Included patients were 18 yrs or older and were discharged during the study period (2003–2007) with a principal or secondary International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis of severe sepsis as defined by Dombrovskiy et al (Table 1) (4, 5), consisting of an International Classification of Diseases, Ninth Revision, Clinical Modification code for sepsis and an additional code for organ dysfunction. We reviewed several previous definitions of organ dysfunction and compiled them into a single list (Table 2) (2, 3, 5).

For each patient, we recorded age, sex, race, and principal and secondary diagnoses (up to 15 diagnoses total). Using software provided by Agency for Healthcare Research and Quality, we recorded the presence of 25 comorbid conditions; additionally, we used diagnosis codes to assess the source and type of infection (21). Primary outcomes included changes in population incidence, number of hospitalizations, length of stay, in-hospital mortality, and costs of care. Secondary outcomes included the change in the demographics of patients with severe sepsis over time, number and type of organ dysfunction, and discharge disposition. We used NIS-defined categories to report discharge disposition.

Analyses. We calculated the weighted frequency of hospitalized patients using codes provided from the Healthcare Cost and Utilization Project Web site. Using population estimates for years 2003 to 2007, we used direct standardization (as recommended by Healthcare Cost and Utilization Project) (17) to calculate age- and sex-adjusted population incidence and mortality rates for severe sepsis per 100,000 population for the years 2003 to 2007. This method for calculating population incidence and mortality rates assumes that all cases of severe sepsis in the United States were treated in a hospital.

We defined in-hospital mortality as the number of deaths divided by total number of severe sepsis hospitalizations. We used indirect standardization to adjust in-hospital mortality rates for age, sex, race/ethnicity, and comorbid conditions; we used logistic regression models from 2003 to predict in-hospital mortality for 2004 to 2007. We tested for linear trends in rates over time and compared trends between subgroups of patients.

Following NIS recommendations, we calculated costs using hospital-specific cost-to-charge ratios when available (≈75% of hospitals) and used a weighted group average at the state level for remaining hospitals. We converted all costs to 2007 dollars using the Consumer Price Index. Because costs were not normally distributed, we calculated both the arithmetic and the weighted geometric mean of costs. The geometric mean is the average of the logarithmic values of a data set, which is then converted back to a base-ten number. It is less strongly influenced by extreme values than the arithmetic mean. We calculated standard errors using a Taylor series expansion. We estimated total costs as a weighted sum of patient-level costs and adjusted to account for missing cost data, which varied by year from 15.4% in 2003 to 2.7% in 2007. We assessed cost trends over time using simple linear regression and considered $p < 0.05$ to be statistically significant; all tests were two-sided. All analyses accounted for sampling weights and were performed using SAS statistical software (version 9.1; SAS, Cary, NC).

RESULTS

We identified a total of 161,140,024 (SD = 2,682,172) hospitalizations among adult patients in the United States between 2003 and 2007 (Fig. 1). Of these, 4,799,565 (SD = 91,378, 2.98% of overall hospitalizations) had a code indicating a diagnosis of sepsis and, of these, 2,899,917 (SD = 56,900; 1.76% of all hospitalizations overall) had an additional code for organ dysfunction, qualifying these patients for a diagnosis of severe sepsis (Table 3). There was a rapid steady increase in the number of hospitalized cases of severe sepsis, from 415,280 in 2003 to 711,736 in 2007 (a 71% increase), an annual growth rate of 17.8% per year. After adjusting for age and sex, the population incidence of severe sepsis increased from 200 (SE = 5) cases per 100,000 in 2003 to 300 (SE = 7) cases per 100,000 in 2007 (a 50% increase; $p < .0001$) (Table 4).

Across the 5-yr period, there were statistically significant changes in the age and gender of patients with sepsis, but these changes do not appear to represent clinically important changes in the population of patients with sepsis (Table 5).

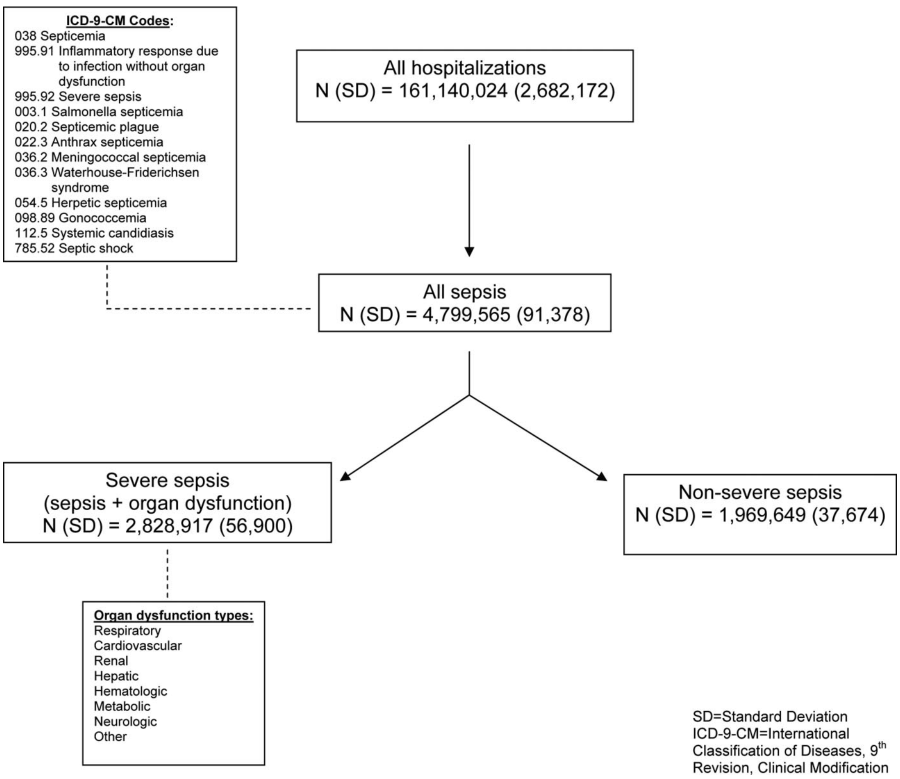

Figure 1. Cases of sepsis and severe sepsis in the United States from 2003 to 2007.

Table 3. Hospitalizations and costs for severe sepsis, 2003 to 2007

	2003 N (SD)	2004 N (SD)	2005 N (SD)	2006 N (SD)	2007 N (SD)	p^a
All hospitalizations	31,634,852 (531013)	31,924,643 (526286)	32,072,881 (601682)	32,791,342 (610282)	32,716,306 (578396)	<.001
All Sepsis hospitalizations	799,155 (19404)	884,339 (20199)	955,536 (25157)	1,045,423 (24849)	1,115,112 (24951)	<.001
Non-severe sepsis hospitalizations	383,875 (9781)	385,944 (9207)	388,514 (10771)	407,940 (10800)	403,376 (10059)	<.001
Severe sepsis						
Hospitalizations	415,280 (10429)	498,395 (12129)	567,022 (15535)	637,483 (15486)	711,736 (16412)	<.001
Deaths	154,159 (4188)	174,337 (4537)	190,002 (5083)	201,627 (4793)	207,427 (5009)	<.001
Total cost (2007 billion U.S. dollars)	15.4 (0.7)	17.2 (0.6)	19.7 (0.7)	21.0 (0.5)	24.3 (0.8)	0.001
Mean cost/case (2007 U.S. dollars)						
Geometric mean[b]	20,210 (407)	19276 (333)	19391 (339)	19129 (251)	19,330 (344)	0.025
Arithmetic mean[b]	37,161 (895)	34420 (721)	34745 (771)	32878 (461)	34,142 (782)	0.0075
Mean length of stay/case (days)						
Geometric mean[b]	9.9 (0.1)	9.5 (0.1)	9.4 (0.1)	9.3 (0.1)	9.2 (0.1)	<.001
Arithmetic mean[b]	15.6 (0.2)	15 (0.2)	14.7 (0.2)	14.5 (0.2)	14.2 (0.2)	<.001

[a]Test for linear trend across year; [b]standard error from Taylor series expansion.

Table 4. Cases of severe sepsis per 100,000 population; age 18 years and older, 2003 to 2007[a]

	2003 N (SE)	2004 N (SE)	2005 N (SE)	2006 N (SE)	2007 N (SE)	p^b
Hospitalizations						
Overall	200 (5)	236 (6)	263 (7)	273 (7)	300 (7)	<.001
Male	199 (5)	237 (6)	261 (7)	278 (7)	308 (7)	<.001
Female	201 (5)	235 (6)	265 (8)	269 (7)	292 (7)	<.001
18–64	83 (2)	99 (3)	107 (3)	117 (3)	130 (3)	<.001
65–84	647 (17)	768 (19)	862 (25)	919 (24)	998 (24)	<.001
85+	1771 (58)	2011 (59)	2343 (90)	1995 (61)	2197 (76)	0.086
White	142 (4)	169 (5)	201 (7)	193 (7)	209 (6)	<.001
Black	229 (19)	291 (22)	246 (17)	311 (23)	329 (24)	.002
Hispanic	153 (14)	150 (14)	174 (15)	202 (18)	198 (16)	<.001
Other	153 (15)	173 (17)	193 (14)	208 (19)	253 (20)	<.001
In-hospital Mortality						
Overall	75 (2)	83 (2)	89 (2)	86 (2)	87 (2)	.004
Male	74 (2)	83 (2)	87 (2)	87 (2)	89 (2)	<.001
Female	76 (2)	83 (2)	91 (3)	85 (2)	85 (2)	.088
18–64	25 (1)	28 (1)	28 (1)	29 (1)	30 (1)	<.001
65–84	256 (7)	286 (7)	306 (8)	311 (8)	310 (8)	<.001
85+	818 (28)	886 (26)	993 (38)	802 (24)	808 (29)	.641
White	55 (2)	61 (2)	70 (3)	64 (2)	62 (2)	.200
Black	88 (8)	103 (8)	79 (5)	96 (7)	94 (7)	.832
Hispanic	58 (5)	53 (5)	56 (5)	63 (6)	59 (6)	.183
Other	61 (6)	62 (6)	67 (5)	67 (6)	79 (7)	<.001

[a]Standardized to 2000 U.S. census population; [b]p values for slope across year.

For example, the proportion of women with severe sepsis decreased from 50% to 49%, and the proportion of patients aged 65–84 decreased from 48% to 46%. The racial/ethnic makeup (white, 67%; black, 16%; Hispanic, 10%; other, 7%) of patients with severe sepsis did not change significantly. Among patients with severe sepsis, women tended to be older than men (69 yrs vs. 67 yrs; $p < .001$) and whites tended to be older than blacks or Hispanics (70 yrs vs. 63 yrs and 64 yrs; $p < .001$).

We observed clinically and statistically significant changes in the prevalence of organ dysfunction during the study period. The proportion of all sepsis cases without documented organ dysfunction (nonsevere sepsis) decreased from 48% in 2003 to 36% in 2007 ($p = .0018$) (Fig. 2). Among patients with severe sepsis (Table 5), the proportion of patients with severe sepsis and one organ dysfunction decreased from 51% in 2003 to 45% in 2007 ($p < .0001$), whereas the proportion of patients with two organ dysfunctions did not change ($p = .85$), and the proportion of patients with three or four or more organ dysfunctions increased 1.19-fold and 1.51-fold, respectively ($p < .0001$). The rate of increase was not equally distributed by type of organ dysfunction (Fig. 3). The proportion of patients with renal failure increased 41% to 49% (an increase of 2.1% per year; $p < .0001$). The proportion of patients with cardiovascular dysfunction (including hypotension, shock, and cardiac arrest) increased from 41% to 46% ($p < .0001$). In contrast, the proportion of patients with respiratory dysfunction did not change significantly during the study time period ($p = .38$). The number of patients per 100,000 with renal dysfunction who received hemodialysis increased slowly over the study timeframe, whereas the number of patients with renal dysfunction who did not receive hemodialysis increased precipitously between 2003 and 2007 (Fig. 4).

The number of in-hospital deaths from severe sepsis (unadjusted for changes in population) increased significantly during the 5-yr period, from 154,159 deaths in 2003 to 207,427 deaths in 2007 (a 35% increase; $p < .0001$) (Table 5). Standardized to the population (Table 4), deaths increased from 75 per 100,000 in 2003 to 87 per 100,000 in 2007, a 16% increase ($p = .004$). We saw statistically significant increases in mortality rates among men and patients younger than 85 yrs. Blacks had consistently higher rates of death compared to whites, Hispanics, and other race/ethnicities (in 2007, 94 deaths/100,000 population). This exceeded the death rates of whites by 32 deaths per 100,000 population per year ($p < .0001$). Despite slightly increasing mortality rates at a population level, adjusted in-hospital mortality declined from 37% in 2003 to 29% in 2007 ($p = .0003$) (Fig. 5). Length of stay decreased significantly during the study timeframe, from 9.9 days per patient in 2003 to 9.2 days per patients in 2007 ($p < .0001$). We observed a corresponding increase in discharge to nursing facilities (which includes inpatient hospice) from 29% of hospitalizations in 2003 to 35% of hospitalizations in 2007 ($p < .0001$).

Total hospital costs for all patients with severe sepsis increased from \$15.4 billion to \$24.3 billion between 2003 and 2007 (57% increase) (Table 3), but we observed a slight decrease in the geometric mean cost per case (\$20,210 in 2003 to \$19,330 in 2007; $p = .025$). In contrast, we found that the geometric mean cost per case for all hospitalizations in the NIS database was \$5,653 in 2003, increasing to \$6,110 in 2007 ($p = .024$). To better-illustrate the change in cost over time for sepsis (including both severe and nonsevere sepsis), severe sepsis, and nonsevere sepsis, we plotted the proportional change in geometric mean of cost per case relative to 2003 for all three conditions (Fig. 6). We also plotted proportional change of hospital mortality relative to 2003 for all three conditions (Fig. 7).

DISCUSSION

Between 2003 and 2007, there was a 71% increase in the number of hospitalizations for severe sepsis and a 57% increase in hospital costs. Although the number of cases of severe sepsis was increasing, in-hospital mortality rates declined substantially, and geometric mean cost per case declined slightly.

The 71% increase in hospitalizations for severe sepsis during the study period greatly exceeds expectations defined by previous studies. For example, Martin (3) reported an annual increase in severe and nonsevere sepsis cases of 8.7% annually between 1979 and 2000. Similarly, using data from 1993 to 2003, Dombrovskiy (5) reported an 8.2% average annual increase in hospitalizations for severe sepsis. In contrast, between 2003 and 2007, we observed a 17.8% average annual increase in hospitalizations for severe sepsis. This increase was driven by an increase in both the number of patients with a diagnosis of sepsis and by an increase in the proportion of patients with organ dysfunction, based on our findings that the average number of organ dysfunctions per patient increased significantly and the proportion of patients with sepsis

Table 5. Hospitalizations for severe sepsis by patient characteristics, 2003 to 2007

	2003 N (%)	2004 N (%)	2005 N (%)	2006 N (%)	2007 N (%)	*p* for trend	Change per year (%)
Gender							
Male	205,779 (50)	249,183 (50)	281,338 (50)	318,489 (50)	359,836 (51)	.005	0.20
Female	209,487 (50)	249,160 (50)	285,660 (50)	318,994 (50)	351,838 (49)	.005	—
Age							
18–64	154,786 (37)	188,366 (38)	208,075 (37)	238,431 (37)	269,195 (38)	.459	0.07
65–84	197,270 (48)	236,087 (47)	268,552 (47)	298,332 (47)	328,573 (46)	.001	−0.33
85+	63,225 (15)	73,943 (15)	90,396 (16)	100,719 (16)	113,968 (16)	.008	0.25
Race/Ethnicity							
White	210559 (66)	255055 (67)	310579 (71)	324158 (67)	358,942 (67)	.568	0.21
Black	53,460 (17)	69,251 (18)	59,713 (14)	80,712 (17)	86,920 (16)	.490	−0.26
Hispanic	34,904 (11)	34,985 (9)	41,539 (10)	51,443 (11)	50,977 (10)	.706	−0.14
Other	18,556 (6)	21,368 (6)	24,538 (6)	28,487 (6)	35,314 (7)	.614	0.19
Organ dysfunctions, number							
1	212,984 (51)	251,667 (51)	282,902 (50)	309,348 (49)	321,629 (45)	<.001	−1.42
2	118,341 (29)	140,518 (28)	158,509 (28)	178,833 (28)	204,236 (29)	.853	0.03
3	57,134 (14)	71,249 (14)	82,758 (15)	96,296 (15)	116,475 (16)	<.001	0.60
4+	26,822 (6)	34,962 (7)	42,852 (8)	53,006 (8)	69,395 (10)	<.001	0.79
Organ dysfunctions, type							
Respiratory	196,488 (47)	229,710 (46)	262,200 (46)	293,027 (46)	331,751 (47)	.379	−0.15
Cardiovascular	169,585 (41)	207,230 (42)	239,151 (42)	275,139 (43)	327,025 (46)	<.001	1.18
Renal	168,830 (41)	212,658 (43)	247,372 (44)	293,661 (46)	350,103 (49)	<.001	2.05
Hepatic	20,879 (5)	25,884 (5)	30,691 (5)	34,240 (5)	38,808 (5)	.555	0.10
Hematologic	79,915 (19)	90,489 (18)	99,070 (17)	107,382 (17)	121,116 (17)	.001	−0.58
Metabolic	61,095 (15)	73,889 (15)	83,957 (15)	100,608 (16)	121,846 (17)	.001	0.58
Neurologic	37,194 (9)	42,674 (9)	48,873 (9)	56,096 (9)	72,674 (10)	.113	0.27
Unknown type	1,249 (0)	13,638 (3)	20,948 (4)	23,467 (4)	16685 (2)	.004	0.50
Infection site							
Abdominal	72,312 (17)	89,134 (18)	103,235 (18)	118,194 (19)	138,205 (19)	<.001	0.47
Blood	393,673 (95)	470,224 (94)	548,856 (97)	621,015 (97)	695,674 (98)	<.001	0.90
Bone	5,086 (1)	6,108 (1)	6,403 (1)	7,906 (1)	10,608 (1)	.570	0.06
Central Nervous System	4,395 (1)	5,248 (1)	5,274 (1)	6,136 (1)	6,878 (1)	.780	−0.03
Endocarditis	8,003 (2)	9,126 (2)	9,796 (2)	11,050 (2)	11,394 (2)	.432	−0.08
Genitourinary	130,855 (32)	162,416 (33)	190,260 (34)	221,033 (35)	263,730 (37)	<.001	1.32
Respiratory	147,179 (35)	172,460 (35)	201,894 (36)	228,682 (36)	267,348 (38)	<.001	0.55
Wound/Soft tissue	25,608 (6)	30,794 (6)	37,195 (7)	43,891 (7)	52,120 (7)	.002	0.30
No known site	1,837 (0)	1,836 (0)	1,727 (0)	1,707 (0)	1,632 (0)	0.591	−0.05
Disposition							
Home	81,310 (20)	87807 (18)	102,565 (18)	1168,58 (18)	136,143 (19)	0.730	−0.04
Transfer	16,786 (4)	20651 (4)	23,265 (4)	27,466 (4)	31,661 (4)	0.461	0.09
Rehabilitation	120,853 (29)	159235 (32)	186,218 (33)	215,667 (34)	249,294 (35)	<.001	1.34
Home Nursing	37,105 (9)	52681 (11)	60,730 (11)	71,559 (11)	82,064 (12)	<.001	0.57
Death	154,159 (37)	174337 (35)	190,003 (34)	201,627 (32)	207,427 (29)	<.001	−1.98
Unknown	2,279 (1)	3236 (1)	3,744 (1)	4,021 (1)	4,824 (1)	0.847	0.02

without organ dysfunction declined significantly during the study period.

The apparent increase in the number of organ dysfunctions contrasts sharply with our findings that geometric mean cost per severe sepsis case and in-hospital mortality rates were decreasing. The decreasing in-hospital mortality was similar to the findings of previous authors, although our rate of decline was more rapid. Dombrovskiy et al (5) reported that in-hospital mortality decreased from 45% in 1993 to 37% in 2003, a decrease of 0.8% per year, whereas we observed an average decline in hospital mortality of 2% per year. To our knowledge, there have been no recent studies examining trends in cost of care for patients with severe sepsis. Using a broad definition of sepsis (including many more codes for infection), Angus et al (2) estimated 750,000 cases nationwide and a cost of $17 billion for a single year (in 1995 dollars). Using a narrower definition, we observed an increase in cost (in 2007 dollars) from $15.4 billion (415,280 cases) in 2003 to $24.3 billion (711,736 cases) in 2007.

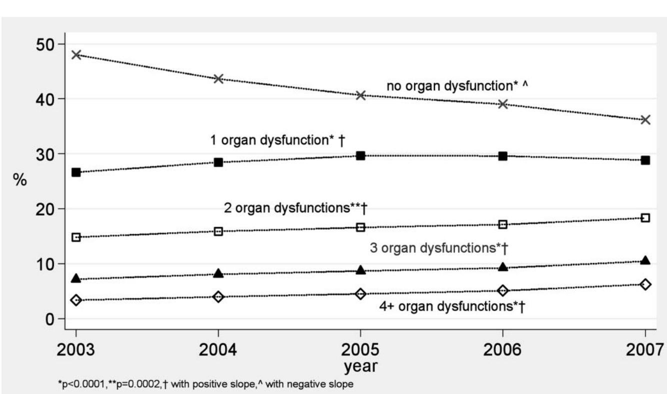

Figure 2. Proportion of patients with sepsis by number of documented organ dysfunctions from 2003 to 2007.

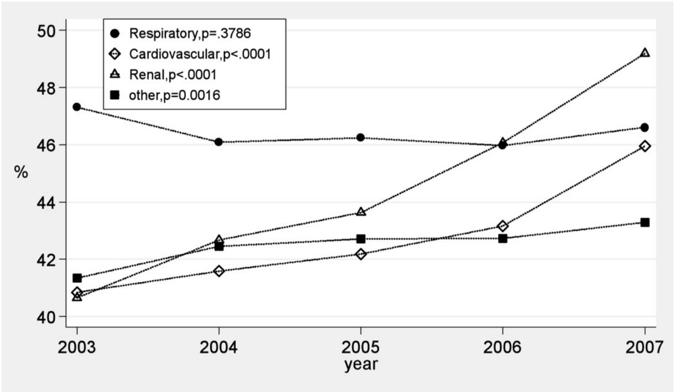

Figure 3. Percentage of severe sepsis cases with each type of organ dysfunction from 2003 to 2007.

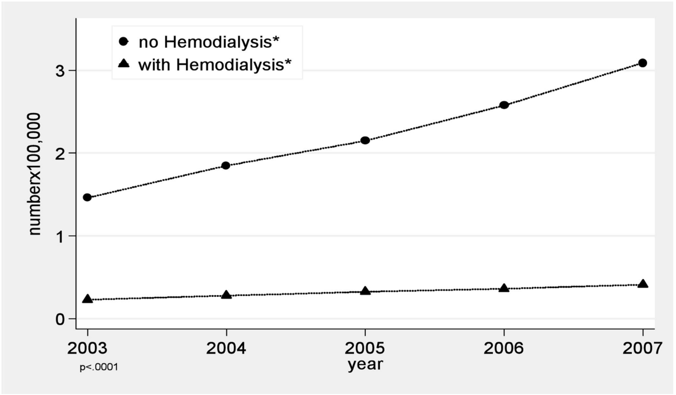

Figure 4. Rates of hemodialysis use among patients with renal dysfunction from 2003 to 2007.

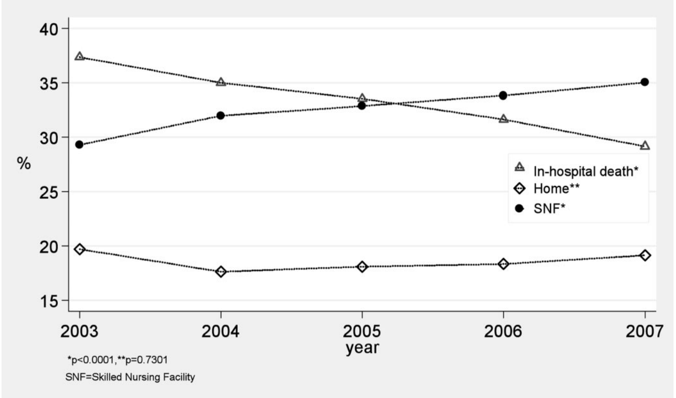

Figure 5. Discharge disposition among patients with severe sepsis, 2003 to 2007.

This increase was driven almost entirely by volume of cases, because the geometric mean cost per case (despite apparent increasing severity) declined slightly during the study timeframe.

Taken together, our findings seem paradoxical. If patients with severe sepsis are getting sicker, then why is the geometric mean cost per case and in-hospital mortality decreasing? One possibility is that declining hospital mortality reflects improvements in care. In the late 1990s, there were several significant changes in the management of sepsis (e.g., a shift away from maximizing cardiac output and the adoption of mechanical ventilation techniques that protect the lungs) (22–25). Activated protein C became available in 2003; however, its use has remained limited (≈6% of patients with severe sepsis in the intensive care unit receive activated protein C) (26). Early goal-directed therapy was introduced in 2001 (27) but did not come into widespread use until the introduction of the "sepsis bundle" between 2005 and 2008 (28, 29). The beginning of the decline in hospital mortality that we observed preceded this timeframe. An alternative explanation for our findings is the increase we observed in the proportion of patients discharged to nursing facilities (including hospice), because some of these patients may have stayed in the hospital until death (30, 31).

However, given the rapid increase in number of cases of sepsis and amount of organ dysfunction, change in discharge disposition does not fully explain our findings. A likely additional contributor to the rapid increase in number of cases, apparent increase in severity, declining geometric mean cost per case, and decreasing hospital mortality rates is changes in documentation and coding of sepsis and organ dysfunction by hospitals. This might be linked to financial incentives for coding of renal and other organ dysfunction. As documentation and coding of sepsis and organ dysfunction changed, additional patients met the criteria for severe sepsis, and these patients were less severely ill than in the past. Several of our findings support this hypothesis. First, we observed a decline in the proportion of patients with sepsis without organ dysfunction. Second, we observed an increase in coding of specific organ dysfunctions, which may be more subject to variation between physicians in the threshold for diagnosis (e.g., renal failure, as indicated by decreased glomerular filtration rate; as seen in Fig. 4, the rapid increase in coding for renal dysfunction was not accompanied by a corresponding increase in hemodialysis use, indicating declining severity). We did not observe an increase in organ dysfunction for which the threshold for diagnosis is clearer (e.g., a lack of increase in proportion of cases with respiratory failure, defined by a code for respiratory failure or use of mechanical ventilation). The disproportionate increase in codes for renal failure is particularly interesting because diagnosis of minor renal dysfunction (particularly in the elderly) requires calculation of glomerular filtration rate by the physician. During the study period, many hospitals were adopting health information technology that would complete this calculation for each patient automatically, saving the clinicians a step, which may have led more clinicians to document the presence of mild renal dysfunction.

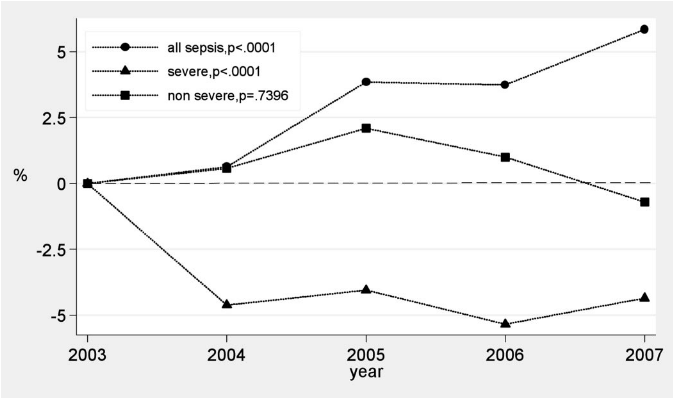

Figure 6. Proportional change in geometric mean of cost per case (relative to 2003) for all, severe, and nonsevere sepsis.

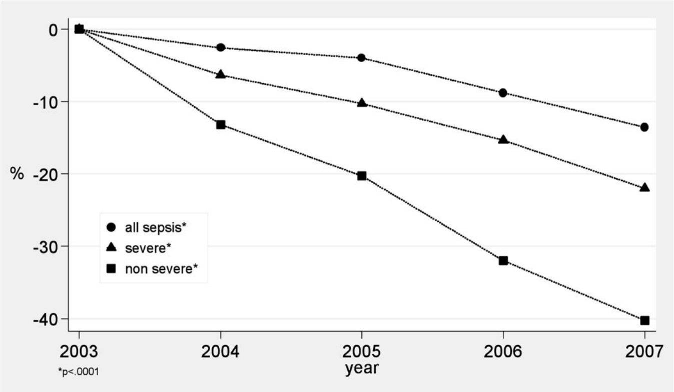

Figure 7. Proportional change in hospital mortality (relative to 2003) for all, severe, and nonsevere sepsis.

Third, we observed declining geometric mean costs per case during the study period. This finding is inconsistent with overall hospital spending trends in the United States between 2003 and 2007; the rate of hospital spending per case increased quite rapidly for most conditions during the study period (20). For example, we observed an increase in mean geometric mean cost per case for all hospitalizations (not just severe sepsis) from $5,653 in 2003 to $6,110 in 2007. At first glance, our findings contradict that of Rothberg et al (20), who, in a study also using NIS data, reported that between 2000 and 2004 cost per case (after adjustment for inflation) increased by 41%, from $9,073 to $12,792. However, they reported on all sepsis, not just sepsis with organ dysfunction. When we included all sepsis cases (Fig. 5), we also found that the geometric mean cost per case of sepsis was increasing, whereas the geometric mean cost per case of both severe and nonsevere sepsis was flat or declining. How can this be? As detection of organ dysfunction increased, the sickest and highest-cost patients in the nonsevere sepsis category were removed from this category, causing the average geometric mean cost of a case of nonsevere sepsis to decline. Those same patients, who were not as sick as the average patient with a case severe sepsis, were added to the severe sepsis category, bringing down the geometric mean cost per case for severe sepsis as well. Figure 6 demonstrates the same phenomenon for mortality.

Our study has several limitations. NIS allows up to 15 diagnosis codes for every hospitalization, but we may have missed some patients with sepsis who had sepsis listed after the first 15 diagnoses. However, because sepsis is an important diagnosis for reimbursement, we would expect few patients to have it listed after diagnosis number 15. NIS is also missing some data on race and ethnicity. We imputed costs for 25% of hospitals based on weighted hospital cost-to-charge ratios. Because 30-day or 60-day mortality is not available in NIS, we used in-hospital mortality as our outcome. Finally, we limited our definition of severe sepsis to a sepsis code plus organ dysfunction (2, 3, 32). Using the narrower definition may have reduced the likelihood that we included patients without sepsis, but it may mean that we missed some cases of sepsis.

In conclusion, the number of cases of severe sepsis appears to have increased dramatically over the span of 5 yrs, but we observed a sharp decline in mortality and declining geometric mean cost per case during the same period. Among several possible explanations for this paradoxical finding, the most likely is changes in documentation and coding practices by hospitals, whereby patients with less severe illness increasingly received codes for sepsis and organ dysfunction. These findings suggest that it is becoming more challenging to use International Classification of Diseases, Ninth Revision, Clinical Modification codes to assess the actual burden of severe sepsis in the United States. Better methods for estimating of the number of U.S. cases of severe sepsis (and for estimating the future demand for critical care resources by sepsis patients) are needed in the future.

ACKNOWLEDGMENTS

The authors acknowledge Nicholas Hannon for his assistance with creating tables and figures, and acknowledge Hilary Price for her assistance with figures.

REFERENCES

1. Abraham E, Singer M: Mechanisms of sepsis-induced organ dysfunction. *Crit Care Med* 2007; 35:2408
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
3. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
4. Dombrovskiy VY, Martin AA, Sunderram J, et al: Facing the challenge: decreasing case fatality rates in severe sepsis despite increasing hospitalizations. *Crit Care Med* 2005; 33: 2555–2562
5. Dombrovskiy VY, Martin AA, Sunderram J, et al: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Critical Care Medicine* 2007; 35:1244–1250
6. Angus DC, Kelley MA, Schmitz RJ, et al: Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: Can we meet the require-

ments of an aging population? *JAMA* 2000; 284:2762–2770
7. Halpern NA, Pastores SM: Critical care medicine in the United States 2000–2005: An analysis of bed numbers, occupancy rates, payer mix, and costs. *Crit Care Med* 2010; 38:65–71
8. Halpern NA, Pastores SM, Thaler HT, et al: Critical care medicine use and cost among Medicare beneficiaries 1995–2000: Major discrepancies between two United States federal Medicare databases. *Crit Care Med* 2007; 35: 692–699
9. Cooper LM, Linde-Zwirble WT: Medicare intensive care unit use: Analysis of incidence, cost, and payment. *Crit Care Med* 2004; 32: 2247–2253
10. Iwashyna TJ: Critical care use during the course of serious illness. *Am J Respir Crit Care Med* 2004; 170:981–986
11. Kahn JM: Understanding economic outcomes in critical care. *Curr Opin Crit Care* 2006; 12:399–404
12. Kahn JM, Angus DC: Reducing the cost of critical care: new challenges, new solutions. *Am J Respir Crit Care Med* 2006; 174: 1167–1168
13. Kahn JM, Brake H, Steinberg KP: Intensivist physician staffing and the process of care in academic medical centres. *Qual Saf Health Care* 2007; 16:329–333
14. Luce JM, Rubenfeld GD: Can health care costs be reduced by limiting intensive care at the end of life? *Am J Respir Crit Care Med* 2002; 165:750–754
15. Pronovost P, Angus DC: Economics of end-of-life care in the intensive care unit. *Crit Care Med* 2001; 29:N46–N51
16. Berenson R: Intensive care units: Clinical outcomes, costs, and decision making. Washington, DC, Office of Technology Assessment prepared for US Congress. 1984. Available at: http://www.cms.hhs.gov/CostReports/. Accessed March 2, 2011
17. HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP) [Internet]. Rockville, MD: Agency for Healthcare Research and Quality, 2003. Available at: http://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed March 2, 2011
18. Wiener RS, Welch HG: Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. *JAMA* 2007; 298:423–429
19. Bateman BT, Schmidt U, Berman MF, et al: Temporal trends in the epidemiology of severe postoperative sepsis after elective surgery: A large, nationwide sample. *Anesthesiology* 2010; 112:917–925
20. Rothberg MB, Cohen J, Lindenauer P, et al: Little evidence of correlation between growth in health care spending and reduced mortality. *Health Aff (Millwood)* 2010; 29: 1523–1531
21. Elixhauser A, Steiner C, Harris DR, et al: Comorbidity measures for use with administrative data. *Medical Care* 1998; 36:8–27
22. Hayes MA, Timmins AC, Yau EH, et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722
23. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med* 1995; 333:1025–1032
24. Slutsky AS, Tremblay LN: Multiple system organ failure. Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med* 1998; 157:1721–1725
25. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342: 1301–1308
26. Ferrer R, Artigas A, Suarez D, et al: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009; 180: 861–866
27. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
28. Levy MM, Pronovost PJ, Dellinger RP, et al: Sepsis change bundles: Converting guidelines into meaningful change in behavior and clinical outcome. *Crit Care Med* 2004; 32: S595–S597
29. Levy MM, Dellinger RP, Townsend SR, et al: The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010; 36: 222–231
30. Kahn JM, Benson NM, Appleby D, et al: Long-term acute care hospital utilization after critical illness. *JAMA* 2010; 303: 2253–2259
31. Unroe M, Kahn JM, Carson SS, et al: One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: A cohort study. *Ann Intern Med* 2010; 153:167–175
32. Angus DC, Wax RS: Epidemiology of sepsis: An update. *Crit Care Med* 2001; 29: S109–S116