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Original Research

CRITICAL CARE

Nationwide Trends of Severe Sepsis in the 21st Century (2000-2007)

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Background: **Severe sepsis is common and often fatal. The expanding armamentarium of evidence-based therapies has improved the outcomes of persons with this disease. However, the existing national estimates of the frequency and outcomes of severe sepsis were made before many of the recent therapeutic advances. Therefore, it is important to study the outcomes of this disease in an aging US population with rising comorbidities.**

Methods: **We used the Healthcare Costs and Utilization Project's Nationwide Inpatient Sample (NIS) to estimate the frequency and outcomes of severe sepsis hospitalizations between 2000 and 2007. We identified hospitalizations for severe sepsis using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes indicating the presence of sepsis and organ system failure. Using weights from NIS, we estimated the number of hospitalizations for severe sepsis in each year. We combined these with census data to determine the number of severe sepsis hospitalizations per 100,000 persons. We used discharge status to identify in-hospital mortality and compared mortality rates in 2000 with those in 2007 after adjusting for demographics, number of organ systems failing, and presence of comorbid conditions.**

Results: **The number of severe sepsis hospitalizations per 100,000 persons increased from 143 in 2000 to 343 in 2007. The mean number of organ system failures during admission increased from 1.6 to 1.9 ($P < .001$). The mean length of hospital stay decreased from 17.3 to 14.9 days. The mortality rate decreased from 39% to 27%. However, more admissions ended with discharge to a long-term care facility in 2007 than in 2000 (35% vs 27%, $P < .001$).**

Conclusions: **An increasing number of admissions for severe sepsis combined with declining mortality rates contribute to more individuals surviving to hospital discharge. Importantly, this leads to more survivors being discharged to skilled nursing facilities and home with in-home care. Increased attention to this phenomenon is warranted.**

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Abbreviations: ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; LOS = length of hospital stay; NIS = Nationwide Inpatient Sample; SNF = skilled nursing facility

Severe sepsis, the presence of the systemic inflammatory response syndrome caused by an infection with at least one acute organ failure, is a common reason for hospitalization.[1] Mortality rates for severe sepsis far exceed those of common medical conditions such as myocardial infarction and stroke. The aging population of the United States, increased use of chemotherapy, and growing number of patients living with transplants are all likely to increase the frequency of this disease. Moreover, medical advances allow an ever-increasing number of persons with multiple or severe chronic diseases to survive into old age. These factors are also associated with an increased risk of organ failure and death.[2]

Fortunately, the past decade has seen many advances in the management of severe sepsis. Improved understanding of the pathophysiology of severe sepsis has led to rigorous trials that have resulted in changes in the practice and evolution of care of patients with severe sepsis.[3-16]

Previous work has demonstrated that hospitalizations for severe sepsis are expensive and increasingly common.[17,18] However, because these studies were conducted prior to the many recent advances in research and practice, national estimates of the net effect of these therapies on an aging, higher-risk population are unavailable. It is important to identify trends of severe sepsis and its mortality in this era in order to appropriately allocate resources for research and policy making and to determine if the expected benefits of improved therapies are being realized.

Therefore, we used the Healthcare Costs and Utilization Project's Nationwide Inpatient Sample (NIS) to estimate national trends in the frequency and outcomes of hospitalizations for severe sepsis in the United States between 2000 and 2007. We hypothesized that, whereas the incidence of severe sepsis rose during this period, mortality improved, particularly if one accounts for an expected increase in the level of comorbidity.[19,20] We also hypothesized that older, sicker individuals who survive severe sepsis are more likely to be functionally dependent after discharge. Therefore, we also describe changes in the discharge destinations of persons surviving their hospital stay.

Materials and Methods

Data Source

NIS is the largest all-payer inpatient-care database publicly available in the United States. It is an administrative data set created by the Agency for Healthcare Research and Quality from data contributed by participating states. During the study years, it contained data on 5 to 8 million hospital stays from about 1,000 hospitals sampled to approximate a 20% sample of US community hospitals, defined by the American Hospital Association to be "all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions."[21] Thus, specialty hospitals, public hospitals, and academic medical centers are included. The NIS is a stratified probability sample of hospitals from this frame, with sampling probabilities proportional to the number of US community hospitals in each stratum. The strata use five hospital characteristics: ownership/control, bed size, teaching status, urban/rural location, and US region. The sample of hospitals included each year is independent of the sample included in preceding years.

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All discharges from sampled hospitals are included in the NIS database. Each hospitalization is treated as an individual entry in the database and is coded with one principal diagnosis, up to 14 secondary diagnoses, and 15 procedures associated with that stay. The NIS includes all hospitalizations, regardless of payer. It also includes information on hospital characteristics: teaching status, location, volume, and ownership. Because it does not contain personal identifiers, it is not possible to link multiple hospitalizations to a single person. To facilitate the production of national estimates, both hospital and discharge weights are provided, along with information necessary to calculate the variance of estimates.[21]

Study Population

We used *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes to identify patients aged ≥18 years discharged with severe sepsis between 2000 and 2007. Based on the coding system used and validated previously by Martin et al,[22] we defined severe sepsis as either (1) ICD-9-CM code for systemic inflammatory response syndrome due to infectious process with organ failure or (2) ICD-9-CM code for septicemia, bacteremia, or fungemia and at least one organ failure code. We provide specific codes in e-Tables 1 and 2. We defined the severity of sepsis by the number of organ failures. We also identified the presence of comorbid conditions using standard ICD-9-CM codes (e-Table 3).

Treatment and Outcomes

We used ICD-9-CM procedure codes to identify persons who underwent mechanical ventilation, received blood products, or had new dialysis. We considered that a person received new dialysis if they had a diagnosis of acute renal failure and a procedure code for hemodialysis or venous catheterization for hemodialysis. We identified persons who received activated protein C using the ICD-9-CM code introduced in 2003. We used length of hospital stay (LOS) as recorded in the NIS. We classified discharges as deaths, discharges to home, discharges to skilled nursing facilities (SNFs), discharges with home care, and other. We present details of this classification system in e-Table 3.

Statistical Analysis

We used the weights provided with the NIS to generate national estimates of the number of admissions in each age and sex group during each year. We calculated the number of admissions per 100,000 adults using annual population estimates from the United States Census Bureau (http://factfinder.census.gov). We performed direct standardization with regards to age and sex to compare the incidence of severe sepsis in 2000 and 2007.

We used logistic regression to examine risk factors for in-hospital mortality. We used single-predictor logistic regressions to identify significant associations between putative risk factors and mortality. All variables that were significantly ($P < .05$) associated with mortality in single-predictor analyses were included in the final multiple logistic model. We included variables reported previously to affect outcomes of severe sepsis in the final logistic regression model, even if they did not meet statistical significance. We checked variables for multicollinearity using tolerance and the variance inflation factor. For the variables used in the final model, both the tolerance and the variation inflation factor were very close to unity. To account for interactions among selected variables, we examined interaction terms; we retained those found significant in the model. The final model for mortality was adjusted for age, sex, race, hospital characteristics, and the presence or absence of specific organ failures and comorbid conditions (diabetes mellitus, congestive heart failure, COPD, cirrhosis, solid organ transplant, HIV infection, cancer, and end-stage renal disease). A separate multiple logistic regression analysis was performed using the number of organ failures, instead of specific organ failures, to compare mortality between 2000 and 2007 for each number of organ failures. In adjusted analyses, the characteristics and predictors of outcomes of severe-sepsis-related hospitalizations in 2000 and 2007 were compared using asymptotic Z tests. We compared both unadjusted mortality and mortality adjusted for demographics, organ failures, and comorbidities, as well as the hospital characteristics mentioned here.

We also compared LOS across years using asymptotic Z tests. Because the LOS is not normally distributed, we performed our comparisons using the natural log of LOS, which conformed more to a normal distribution. We used Stata IC 11.0 (StataCorp; College Station, Texas) for all analyses. This study was approved by the institutional review board of the Medical College of Wisconsin (MCW/FH Institutional Review Board No. 5, IRB No. PRO00012567).

Results

The annual number of discharges with severe sepsis increased from 300,270 (0.99% of all hospitalizations) in 2000 to 781,725 (2.38% of all hospitalizations) in 2007, amounting to a 160% increase over the span of the study period (e-Fig 1, Fig 1). The frequency of hospitalizations with severe sepsis increased from 143 per 100,000 US adults in 2000 to 343 per 100,000 in 2007, an average annual increase of 16.5%. As shown in Figure 2, the increase was quite consistent throughout this period and occurred among both men and women. The increase was largest in absolute terms among older individuals (≥65 years). However, the difference in frequency was not primarily due to population aging: when normalized to the 2000 age and sex population distribution, the frequency increased from 143 per 100,000 to 328 per 100,000. Similarly, the incidence of septic shock increased 3.2 times.

Characteristics of Severe Sepsis

The demographic and clinical characteristics of patients with severe sepsis are shown in Table 1. The mean number of organ systems failing increased from 1.62 in 2000 to 1.90 in 2007 ($P < .001$). The percentage of hospitalizations for severe sepsis with just one organ failure decreased during this period (58.3% to 47.1%, $P < .001$), whereas the percentage with three or more organ failures increased (15.2% to 24.9%, $P < .001$) (Table 2). The proportion that involved septic shock increased from 30.3% in 2000 to 41.7% in 2007 (Table 1). Respiratory, renal, and cardiovascular failure were the most likely organ system failures throughout the study period, but respiratory failure decreased substantially as a proportion of all cases (52.8%-47.6%), whereas other organ failures either increased considerably (renal, cardiovascular, metabolic) or changed by <2% (hepatic, neurologic, hematologic). Renal failure emerged as the most common organ failure in 2007, whereas respiratory failure predominated in 2000. Secondary to the overall 2.3-fold increase in severe sepsis, all forms of organ failure became more common in absolute terms of population projections (e-Table 4). The distribution of comorbidities was similar in 2000 and 2007, although the proportion of persons admitted for severe sepsis with diabetes, congestive heart failure, and end-stage renal disease increased and the proportion with cirrhosis and HIV decreased.

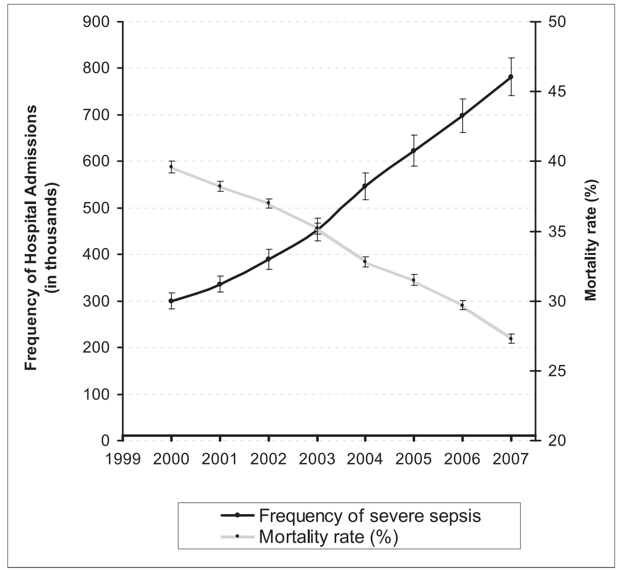

Figure 1. Frequency of admission and mortality rates due to severe sepsis, 2000-2007. Bars represent SEM.

Processes of Care

Rates of mechanical ventilation decreased from 40.9% in 2000 to 35.3% in 2007 ($P < .001$). A similar decline was noticed in the rates of prolonged mechanical ventilation (defined as mechanical ventilation for >96 h in duration). The proportion of hospitalizations with severe sepsis that involved infusion of blood products increased significantly (Table 1).

Outcomes

LOS decreased between 2000 and 2007, both among persons who died and among survivors (Table 2). Overall, in-hospital mortality rates of severe sepsis decreased from 39.6% in 2000 to 27.3% in 2007 (OR, 0.57). As shown in Figure 1, this decrease was consistent throughout the study period. It was even more impressive after adjusting for differences in comorbidities, organ failures, and demographic characteristics: After adjustment, the odds of mortality in 2007 were just 0.46 (95% CI, 0.44-0.49) times the odds in 2000 (e-Table 5). The mortality rates of persons with septic shock declined by 10%. Table 3 shows the results of the survey-design-adjusted multiple logistic regression model examining predictors of mortality of severe sepsis in the years 2000 and 2007.

Although mortality was consistently higher in persons with more organ systems failing, the risk of mortality decreased between 2000 and 2007 for each number of organ systems failing (Tables 2, 4). Despite the decrease in case fatality rate for severe sepsis, the number of severe sepsis hospitalizations ending in death increased nearly 1.8 times, because of the marked increase in the number of severe sepsis hospitalizations. Although more patients survived to hospital discharge, the proportion of patients being discharged home did not change significantly (20.7% in 2000 to 20.2% in 2007). Conversely, there was a significant increase in the proportion discharged to SNF (27.5% in 2000 to 35.3% in 2007) and home care (7.6% in 2000 to 12.1% in 2007).

Discussion

We have demonstrated that the increases in the frequency of severe sepsis through 2000 documented by others have continued, and even accelerated, during the period from 2000 to 2007 (e-Table 6). Moreover, despite remarkable improvements in severity-adjusted mortality during this time frame, the marked increase in hospitalizations has led to a continued striking increase in the number of deaths associated with severe sepsis. Similar trends were observed for septic shock, where the incidence increased 3.2 times and mortality decreased by 10%. In our analysis, severe sepsis accounted for a significant proportion of hospital care; we found that nearly one in 40 hospitalizations (2.38%) during 2007 was for sepsis complicated by organ failure. The combination of increased frequency of severe sepsis hospitalizations and improved mortality has led to a remarkable 3.4-fold increase in the number of patients discharged to SNF following severe sepsis (from 2000 to 2007).

Our results can be compared most readily with those of Martin et al,[22] who used the National Hospital Discharge Survey to demonstrate an increase in the frequency of sepsis hospitalizations from 82.7 per 100,000 population in 1979 to 240.4 per 100,000 population by the year 2000. In 2000, 33.6% of these had severe sepsis, suggesting a frequency of severe sepsis of 80.8 per 100,000. This number is substantially lower than ours, possibly because of differences in the hospitals and patients included (ie, the National Hospital Discharge Survey does not include many hospital types included in the NIS [eg, specialty hospitals and very small hospitals]), which would have led to an underascertainment of cases of severe sepsis. Further, Martin et al[22] included children, whereas we did not. Despite these differences, we reached similar conclusions regarding the mortality of severe sepsis in 2000, the steady upward trend in frequency,

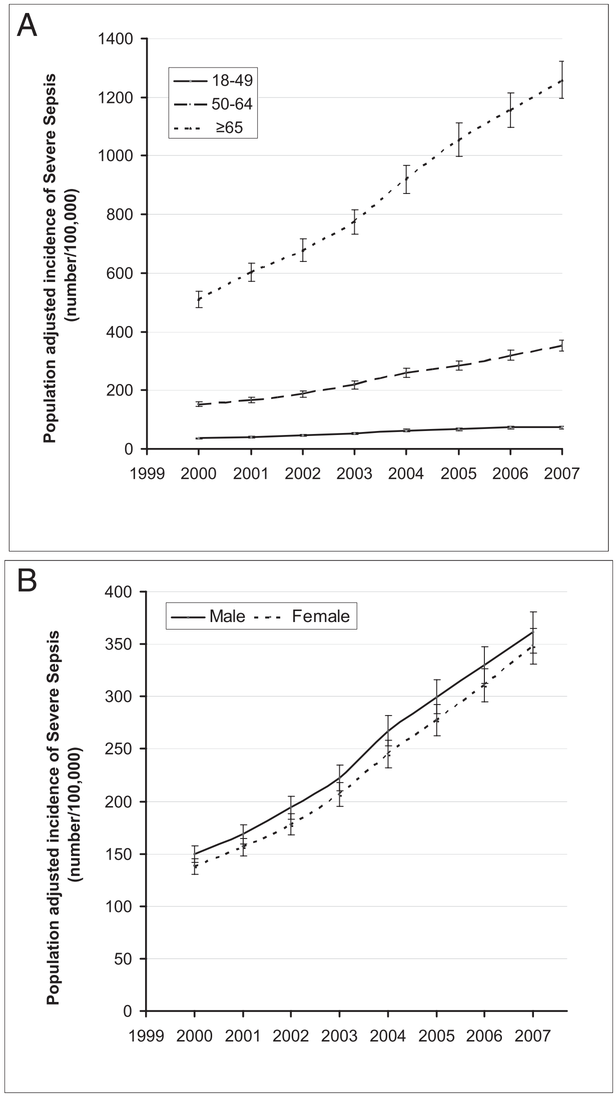

Figure 2. A, Frequency of severe sepsis hospitalizations by age, 2000-2007. B, Frequency of severe sepsis hospitalizations by sex, 2000-2007. Bars represent SEM.

and the steady downward trend in mortality. As with our study, they observed a gradual increase in the age of persons with severe sepsis and number of organ systems failing over the study period. We believe that the accelerated rate of decline in mortality identified in our study (30% over 8 years) may reflect the advent and broad use of therapies directed specifically at severe sepsis and its sequelae during the past decade.[3-9]

Our study can also be compared with that of Angus et al,[17] who estimated a frequency of 300 per 100,000 hospitalizations for severe sepsis in 1995 using hospital discharge databases from seven states. This higher frequency likely reflects use of a much broader universe of codes in their study (1,286 distinct codes). Our estimate of the number of severe sepsis hospitalizations in those ≥ 18 years of age would

Table 1—*Characteristics of Patients With Severe Sepsis in 2000 vs 2007*

Patient Characteristics	2000 (n = 300,270)	2007 (n = 781,725)
Age,[a] No. per 100,000 (% of patients)		
18-49 y[b]	40.2 (15.9)	78.5 (14.7)
50-64 y[b]	167.1 (21.3)	369.5 (24.2)
≥ 65 y[b]	535.8 (62.8)	1,295.7 (61.1)
Sex[a], No. per 100,000 (% of patients)		
Male	159.8 (50.3)	373.7 (50.9)
Female	147.9 (49.7)	342.2 (49.1)
Race[b]		
Non-Hispanic white	16,6801 (55.6)	391,696 (50.1)
Non-Hispanic black	38,903 (13.0)	97,619 (12.5)
Hispanic	20,359 (6.8)	56,995 (7.3)
Asian	5,035 (1.7)	17,765 (2.3)
Other	6,129 (1.9)	20,862 (2.6)
Unknown	63,033 (21.0)	196,788 (25.2)
Procedures		
Mechanical ventilation[b]	122,697 (40.9)	275,736 (35.3)
Mechanical ventilation > 96 h[b]	716,10 (23.8)	160,424 (20.5)
Blood transfusions[b]	51,516 (17.2)	201,666 (25.8)
New dialysis	16,807 (5.6)	46,527 (6.0)
Platelet transfusion[b]	6,866 (2.3)	28,776 (3.7)
Activated protein C[b]	9,921 (2.0)[c]	8,469 (1.1)
Specific organ failure		
Pulmonary[b]	158,416 (52.8)	372,133 (47.6)
Renal[b]	100,434 (33.4)	380,239 (48.6)
Cardiac[b]	90,996 (30.3)	325,620 (41.7)
Hematologic[b]	59,951 (20)	142,261 (18.2)
Metabolic[b]	39,063 (13)	129,913 (16.6)
Neurologic[b]	26,020 (8.7)	82,829 (10.6)
Hepatic[b]	12,127 (4.0)	38,075 (4.9)
Elixhauser comorbidity score[b]		
0	11,242(3.7)	20,012(2.6)
1	41,661 (13.9)	81,626 (10.4)
2	77,171 (25.7)	164,816 (21.1)
3	81,625 (27.3)	197,546 (25.3)
4	53,977 (18.0)	163,634 (20.9)
≥ 5	34,594 (11.5)	154,090 (19.7)
Comorbidities		
Diabetes[b]	62,597 (20.8)	185,618 (23.7)
Congestive heart failure[b]	78,842 (26.3)	219,520 (28.1)
COPD[b]	61,570 (20.5)	165,616 (21.2)
Cirrhosis	22,038 (7.3)	53,914 (6.9)
Solid organ transplant	3,908 (1.3)	11,609 (1.5)
HIV infection	6,189 (2.1)	12,844 (1.6)
Cancer	52,853 (17.6)	135,767 (17.4)
End-stage renal disease[b]	16,602 (5.5)	68,157 (8.7)
Disposition[b]		
Mortality	118,676 (39.6)	213,124 (27.3)
Home	620,05 (20.7)	157,681 (20.2)
Skilled nursing facility	82,311 (27.5)	275,906 (35.3)
Home care	22,895 (7.6)	94,441 (12.1)
Other[d]	13,889 (4.6)	40,225 (5.1)
Mean LOS in survivors,[b] mean ± SE, d	17.3 ± 0.29	14.9 ± 0.27
Mean time to death,[b] mean ± SE, d	14.0 ± 0.35	12.5 ± 0.32

Data are presented as No. (%) unless indicated otherwise. LOS = length of hospital stay.
[a]Prevalence is calculated from 2000 and 2007 census as per United States Census Bureau.
[b]Significant difference at $P < .05$ by χ^2 test; t tests used for LOS comparison.
[c]The code for activated protein C first became available in 2003. The data presented in the table are from 2003.
[d]Includes discharges to short-term hospitals, against medical advice, and unknown.

Table 2—*Mortality in Severe Sepsis by Number of Organ System Failures (Unadjusted Comparison Between 2000 and 2007)*

No. Organ System Failures	2000		2007	
	Frequency (%)	Mortality, %	Frequency (%)	Mortality, %
1[a]	174,956 (58.3)	28.6	36,8123 (47.1)	15.1
2[a]	79,428 (26.5)	48.5	218,641 (28)	28.9
3[a]	33,221 (11.1)	63.2	121,793 (15.6)	42.7
4[a]	10,116 (3.4)	72.0	52,505 (6.7)	54.5
5[a]	2,236 (0.7)	80.0	16,858 (2.2)	65.4
6	303 (0.1)	77.7	3,496 (0.4)	73.6
7	9 (0.003)	49.9	308 (0.04)	74.6

[a]Significant difference between 2000 and 2007 at $P < .05$ by χ^2 test.

increase from 570 per 100,000 population in 2000 to 1,054 per 100,000 population in 2007 if we used their codes (data not shown). Of note, they projected an increase of 1.5% annually simply due to changes in the age structure of the population. Our results, and those of Martin et al,[22] make it clear that the rate of increase is far greater, which has important policy implications.

During the 8 years we studied, the in-hospital mortality of severe sepsis declined steadily, from 39.6% to 27.3%, and that of septic shock from 47.1% to 36.4%. This decline is even more noteworthy if we adjust for the increase in age and severity of disease (eg, number of organs failing). We note that there has been increased attention to appropriate withdrawal of care from critically ill patients with extremely poor prognosis.[23] If this leads to more frequent in-hospital death, the observed reduction is even more remarkable. In addition, this reduction in mortality is more profound considering the fact that administrative databases such as the NIS are unable to capture implementation of advanced directives or changes in goals of care by the provider or family. An upward shift in the trend of such measures is likely, given the incapacitating nature of this severe syndrome in an older, sicker, population. In addition to the nonspecific improvements in ICU care cited by Martin et al,[22] we suspect the decreasing mortality reflects heightened awareness, earlier recognition, and aggressive therapy of sepsis.[24-28]

Survivors experienced a significant increase in the number of discharges to SNF and home health care between 2000 and 2007. Although the proportion of patients being discharged home remained similar, the improvement in mortality between 2000 and 2007 in proportional terms (12.3%) was matched exactly by the number of survivors being discharged either to home health care or SNF. The increasing percentage of discharges to SNF continues the trend observed by Martin et al.[22] They reported an increase from 16.8% of sepsis survivors discharged to SNF in 1978 to 31.8% in 2000. Our results suggest a further increase, from 45.5% in 2000 to 48.6% in 2007. The difference between our estimates for 2000 may reflect their inclusion of children, as well as the fact that we restricted our attention to survivors of severe sepsis, whereas Martin included all individuals surviving sepsis. Our finding of decreased LOS with stable or increasing procedure use reflects an overall trend for the intensity of inpatient care to increase, while LOS decreases. This reflects a rational response by both physicians and hospitals to current payment approaches, particularly those of the Centers for Medicare and Medicaid Services, the dominant US payer.[29,30] This increase in discharges to SNFs and home care has implications for further increases in health-care costs, reimbursement structures, and hospital staffing patterns.

The mean number of organ system failures per patient increased significantly during the study period, as did the proportion of patients with three or more organ failures. These findings suggest that the severity of acute disease associated with hospitalizations for severe sepsis is increasing. We also report the emergence of renal failure as the most common organ failure associated with severe sepsis in 2007, in contrast to respiratory failure, which was the most common in 2000. Although there was a significant rise in the frequency of renal failure complicating severe sepsis, we observed a significant decline in the odds of mortality associated with it. Our observations are consistent with other reports substantiating the increasing frequency of all-cause acute kidney injury in the hospital, with declining mortality trends. More sensitive definitions of acute kidney injury introduced over the past 5 years may have led to more timely recognition and management, which would contribute to the improved survival.

Despite its national scope and use of a widely used, well-characterized database, our study has several important limitations. First, we must acknowledge the limitations of our definition of severe sepsis. As indicated by the different coding strategies chosen by various authors, there is no agreed-upon definition of sepsis or severe sepsis in studies of administrative

Table 3—*Predictors of Mortality in Severe Sepsis in 2000 vs 2007*

Predictor	2000	2007
Age		
18-49 y	Reference	…
50-64 y	1.40 (1.31-1.49)	1.42 (1.34-1.49)
≥65 y	4.43 (4.00-4.91)	5.13 (4.7-5.59)
Sex		
Male	Reference	…
Female	1.05 (1.01-1.09)	1.07 (1.05-1.10)
Race/ethnicity		
White	Reference	…
Black	1.04 (0.97-1.11)	0.99 (0.91-1.06)
Hispanic	0.91 (0.85-1.00)	1.00 (0.92-1.08)
Asian	1.09 (0.95-1.25)	0.94 (0.77-1.13)
Others	1.11 (0.96-1.27)	1.04 (0.93-1.17)
Unknown	0.99 (0.93-1.07)	0.94 (0.87-1.01)
Hospital characteristics		
Nonteaching	Reference	…
Teaching	1.09 (1.01-1.18)	1.02 (0.95-1.10)
Small	Reference	…
Medium	1.08 (0.97-1.19)	0.96 (0.85-1.07)
Large	1.05 (0.95-1.1.15)	0.93 (0.85-1.03)
Rural	Reference	…
Urban[a]	0.98 (0.87-1.07)	0.80 (0.74-0.87)
Specific organ failure		
Respiratory	6.58 (5.98-7.22)	7.23 (6.67-7.84)
Cardiogenic[a]	2.34 (2.17-2.52)	1.97 (1.86-2.08)
Renal[a]	2.07 (1.96-2.18)	1.51 (1.44-1.58)
Hepatic failure	3.87 (2.95-5.09)	2.80 (2.41-3.25)
Hematologic	1.49 (1.37-1.62)	1.41 (1.33-1.50)
Metabolic[a]	2.78 (2.51-3.07)	2.00 (1.85-2.16)
Neurologic[a]	2.37 (2.10-2.67)	1.60 (1.47-1.73)
Comorbid conditions		
Diabetes mellitus[a]	1.03 (0.93-1.15)	0.85 (0.79-0.91)
Congestive heart failure	1.74 (1.55-1.96)	1.56 (1.43-1.70)
COPD	1.08 (0.99-1.18)	1.04 (0.98-1.11)
Cirrhosis	2.31 (1.90-2.80)	2.18 (1.91-2.47)
Solid organ transplant	1.14 (0.90-1.42)	1.03 (0.88-1.22)
HIV infection	2.04 (1.61-2.58)	1.95 (1.61-2.35)
Cancer	3.25 (2.93-3.60)	3.58 (3.34-3.84)
End-stage renal disease[a]	1.12 (0.95-1.31)	1.89 (1.71-2.08)

Data are presented as OR controlling for all other variables in the table (95% CI).
[a]Significant difference between 2000 and 2007 at $P < .05$.

data. Similarly, our choice of codes to characterize organ failure, although identical to those used by Martin et al,[22] may not reliably identify sepsis-related organ failure. Particularly for our analyses of hospital characteristics, we cannot exclude the possibility that variations in coding practices among hospitals led to spurious associations, or obscured real ones. The ICD-9-CM codes are also not static; new codes for severe sepsis and septic shock in 2003 could have influenced our comparisons of 2000 and 2007 data. However, the trends we report were consistent across the study years. Second, despite its strengths, the NIS database has relatively incomplete data regarding race, forcing us to forego comments on the impact of race on severe sepsis frequency and mortality. Because the NIS is a discharge-level database, we are not able to recognize that multiple hospitalizations may have been of the same patient; this may slightly exaggerate the precision of our estimates. It also prevents us from using readmission as an outcome.

Changes in clinical practice could have affected our findings as well. The rising frequency of severe sepsis and septic shock we noted may be due to better recognition and appropriate coding, both of sepsis and of organ failure. As noted previously for renal failure, these changes permit more timely treatment but may increase the average number of failing organ systems coded for each patient. Similarly, the limited clinical detail of our ICD-9-CM codes may not detect important severity differences. For example, different degrees of renal failure cannot be distinguished using these codes. Thus, we cannot comment on whether the improving survival we observed reflects, in part, less severe disease within a type of organ failure.

Information about mortality after discharge is also not available. Thus, mortality that occurs in SNF shortly after discharge from the NIS index hospital would not have been captured in our analysis. If some of the increase in discharges to SNF reflects a reimbursement-driven tendency to manage even severely ill patients in long-term care settings, this could exaggerate the observed decrease in mortality.

Finally, we have limited detail on the processes of care that may have led to the observed changes. For example, we cannot directly link the rise in transfusion rates to increased use of goal-directed therapy protocols. Similarly, we cannot evaluate the contribution of increased use of closed ICUs, 24-hour intensivist coverage, or measures of hospital quality to improved mortality. These are important areas for future research.

Conclusions

Despite its limitations, our study provides an important extension of prior work and suggests future

Table 4—*Predictors of Mortality in Severe Sepsis in 2000 vs 2007 When Number of Organ Failures Is Used Instead of Specific Organ Failures*

No. Organ System Failures	2000	2007
1	Reference	…
2[a]	2.41 (2.30-2.53)	2.06 (1.99-2.14)
3[a]	5.12 (4.67-5.61)	3.66 (3.45-3.89)
4[a]	10.1 (8.67-11.8)	6.38 (5.80-7.03)
5[a]	22.5 (16.9-30.0)	11.1 (9.6-12.7)
6	25.1 (13.0-48.6)	18.3 (14.4-23.3)
7	10.4 (0.50-218)	25.2 (14.2-44.6)

Data are presented as OR controlling for the same variables as in Table 3, except for specific organ failures (95% CI).
[a]Significant difference between 2000 and 2007 at $P < .05$.

directions for research and policy. It reiterates prior warnings that severe sepsis is an increasingly important contributor to hospitalizations, hospital deaths, and, importantly, discharges to SNF. Policy-makers and health-care systems must be ready to meet the needs of this population. Specifically, there is a need to identify approaches that can help the growing cohort of persons discharged to SNF to return to independent living and avoid rehospitalization. These persons are very likely at a high risk of remaining in SNF, because of the debilitating nature of severe sepsis. Measures of the effectiveness of treatment should consider both survival and return to function as important outcomes.

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References

1. Bone RC, Balk RA, Cerra FB, et al; The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101(6):1644-1655.
2. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. *N Engl J Med*. 2002;347(20):1585-1592.
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. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001; 345(19):1359-1367.
5. 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.
6. 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.
7. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
8. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20): 1471-1477.
9. Finfer S, Chittock DR, Su SY, et al; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13): 1283-1297.
10. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock [published correction appears in *JAMA*. 2008;300(14):1652]. *JAMA*. 2002; 288(7):862-871.
11. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J; Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet*. 2000;356(9248):2139-2143.
12. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2008;299(6):637-645.
13. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care*. 2006;10(2):R42.
14. Sands KE, Bates DW, Lanken PN, et al; Academic Medical Center Consortium Sepsis Project Working Group. Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA*. 1997;278(3):234-240.
15. Sundararajan V, Macisaac CM, Presneill JJ, Cade JF, Visvanathan K. Epidemiology of sepsis in Victoria, Australia. *Crit Care Med*. 2005;33(1):71-80.
16. Ferrer R, Artigas A, Levy MM, et al; Edusepsis Study Group. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA*. 2008;299(19):2294-2303.
17. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
18. From the Centers for Disease Control. Increase in National Hospital Discharge Survey rates for septicemia—United States, 1979-1987. *JAMA*. 1990;263(7):937-938.
19. Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123(4):e18-e209.

20. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17): 2038-2047.
21. Introduction to the HCUP nationwide inpatient sample (NIS) 2008. HCUP Web site. http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_2008_INTRODUCTION.pdf. Accessed August 30, 2011.
22. 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.
23. Nelson JE, Angus DC, Weissfeld LA, et al; Critical Care Peer Workgroup of the Promoting Excellence in End-of-Life Care Project. End-of-life care for the critically ill: a national intensive care unit survey. *Crit Care Med*. 2006;34(10):2547-2553.
24. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med*. 2007;35(5):1244-1250.
25. Ferrer R, Artigas A, Suarez D, et al; Edusepsis Study Group. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. *Am J Respir Crit Care Med*. 2009;180(9):861-866.
26. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1): 296-327.
27. 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(2):222-231.
28. Castellanos-Ortega A, Suberviola B, García-Astudillo LA, et al. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. *Crit Care Med*. 2010;38(4):1036-1043.
29. Bohmer RMJ, Newell J, Torchiana DF. The effect of decreasing length of stay on discharge destination and readmission after coronary bypass operation. *Surgery*. 2002;132(1): 10-15.
30. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman MW, Webb SA. Changes in case-mix and outcomes of critically ill patients in an Australian tertiary intensive care unit. *Anaesth Intensive Care*. 2010;38(4):703-709.