Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care

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Objective: To determine the incidence, cost, and outcome of severe sepsis in the United States.

Design: Observational cohort study.

Setting: All nonfederal hospitals (n = 847) in seven U.S. states.

Patients: All patients (n = 192,980) meeting criteria for severe sepsis based on the International Classification of Diseases, Ninth Revision, Clinical Modification.

Interventions: None.

Measurements and Main Results: We linked all 1995 state hospital discharge records (n = 6,621,559) from seven large states with population and hospital data from the U.S. Census, the Centers for Disease Control, the Health Care Financing Administration, and the American Hospital Association. We defined severe sepsis as documented infection and acute organ dysfunction using criteria based on the International Classification of Diseases, Ninth Revision, Clinical Modification. We validated these criteria against prospective clinical and physiologic criteria in a subset of five hospitals. We generated national age- and gender-adjusted estimates of incidence, cost, and outcome. We identified 192,980 cases, yielding national estimates of 751,000 cases (3.0 cases per 1,000 population and 2.26 cases per 100 hospital discharges), of whom 383,000 (51.1%) received intensive care

and an additional 130,000 (17.3%) were ventilated in an intermediate care unit or cared for in a coronary care unit. Incidence increased >100-fold with age (0.2/1,000 in children to 26.2/1,000 in those >85 yrs old). Mortality was 28.6%, or 215,000 deaths nationally, and also increased with age, from 10% in children to 38.4% in those >85 yrs old. Women had lower age-specific incidence and mortality, but the difference in mortality was explained by differences in underlying disease and the site of infection. The average costs per case were $22,100, with annual total costs of $16.7 billion nationally. Costs were higher in infants, nonsurvivors, intensive care unit patients, surgical patients, and patients with more organ failure. The incidence was projected to increase by 1.5% per annum.

Conclusions: Severe sepsis is a common, expensive, and frequently fatal condition, with as many deaths annually as those from acute myocardial infarction. It is especially common in the elderly and is likely to increase substantially as the U.S. population ages. (Crit Care Med 2001; 29:1303–1310)

KEY WORDS: sepsis; severe sepsis; sepsis syndrome; organ failure; intensive care; outcome; resource use; mortality; elderly; epidemiology

Sepsis is a major challenge in medicine. Massive resources have been invested in developing and evaluating potential therapies, and considerable effort has been undertaken to understand the systemic inflammation and multiple-system organ failure characteristics of severe sepsis (1, 2). Yet, information on the incidence, cost, and outcome of sepsis remains scarce and incomplete. In 1990, the Centers for Disease Control (CDC)

estimated that there were 450,000 cases of sepsis per year in the United States, with >100,000 deaths (3). The CDC warned that the incidence was increasing, citing the aging of the U.S. population and the increased prevalence of human immunodeficiency virus (HIV) infection as contributing factors. However, the CDC study counted cases of septicemia, not severe sepsis, which often occurs in patients without positive blood cultures (4–6). Furthermore, this study was based on data from the National Hospital Discharge Survey that are >10 yrs old, provide no information on patient management, and represent only 1% of all hospital discharges.

In 1992, the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference arrived at the current definition of sepsis as a systemic inflammatory syndrome in response to infection which, when associated with acute organ dys-

function such as acute renal failure, is said to be severe (7). These criteria have been adopted widely both in clinical practice and in research. However, there have only been two epidemiologic studies in the United States that used these criteria. One was a single-center study (8), and the other included only eight academic medical centers (9). Neither study included children or provided information on population incidence or costs of care. Therefore, we conducted a study of a large, nationally representative sample to determine estimates of the incidence, associated costs, and outcome of severe sepsis in the United States.

METHODS

Data Sources. We constructed a patient database for calendar year 1995 from seven state hospital discharge databases—Florida (10), Maryland (11), Massachusetts (12), New Jersey (13), New York (14), Virginia (15), and Washington (16). We selected these states

based on their geographic representation, data quality and availability, and inclusion of centers in which we could assess the validity of our selection criteria for severe sepsis. For each case, we extracted the following: demographic characteristics; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for principal discharge diagnosis, ≤14 secondary discharge diagnoses and 15 procedures; hospital discharge status; and selected charge items, listed by both units consumed and dollars charged using the major Health Care Financing Administration (HCFA) UB-92 code categories.

We obtained national and state population data from the U.S. Census (17). The seven-state population in 1995 was 63,497,167, or 25% of the U.S. population. Because the U.S. Census does not report separately the number of infants <1 yr of age, we also obtained the National Center for Health Statistics 1995 natality report (18). We determined hospital characteristics from the 1995 HCFA Provider Specific File (19) and the American Hospital Association (AHA) Guide to the Health Care Field (20).

Case Selection and Definitions. To identify cases with severe sepsis, we selected all acute care hospitalizations with ICD-9-CM codes for both a bacterial or fungal infectious process (Appendix 1) and a diagnosis of acute organ dysfunction (Appendix 2). Classifying acute organ dysfunction is controversial with debate over the choice of measurements and the number of systems to measure. We constructed our system by selecting ICD-9-CM codes suggestive of new onset dysfunction within the six organ systems proposed by Marshall et al. (21) and used by Sands et al (9). We excluded gastrointestinal failure (other than hepatic failure) because it is difficult to define (21, 22).

We organized patient data under the following categories: demographic; infectious etiology; presence of underlying comorbidity, as determined by a Charlson-Deyo score >0 (23); resource use, which included intensive care unit (ICU) use and length of stay (LOS), hospital LOS, and total hospital costs; and hospital mortality. We estimated costs by multiplying reported charges by the hospital-specific cost-to-charge ratios derived from the HCFA Provider Specific File (19). We defined cases as surgical if they had a major surgical procedure other than tracheostomy.

Comparison of ICD-9-CM Selection Criteria to Standard Clinical and Physiologic Criteria for the Definition of Severe Sepsis. Sands et al. (9) prospectively identified a stratified random sample of patients with severe sepsis at eight academic medical centers during 1993 and 1994 using the ACCP/SCCM Consensus clinical and physiologic criteria (7). Our study included 1995 data from five of the eight hospitals. Although Sands et al. (9) did not report individual hospital data by hospital name, we were able to compare aggregate data regarding hospital incidence rates and several patient characteristics to determine the extent to which our ICD-9-CM-based selection criteria identified a similar cohort.

Statistical Analyses. We compared continuous data by the Mann-Whitney U test and categorical data by chi-square or Fisher's exact test as appropriate. We assessed risk factors for hospital mortality by multivariate logistic regression with sequential sum of squares. We generated national estimates using the cohort age- and gender-specific rates. We constructed the databases in Foxpro (Microsoft Corp, Redmond, WA) and conducted analyses in Data Desk (Data Description, Ithaca, NY) and SAS (SAS Institute, Cary, NC).

RESULTS

Comparison of Study Selection Criteria With Prospective Clinical and Physiologic Criteria. Table 1 provides comparative data on the cohort of patients selected by ICD-9-CM criteria with those identified previously by Sands et al (9). Although the ICD-9-CM criteria generated higher occurrence rates, the Sands et al. cohort did not include any floor patients without blood cultures. Baseline and process of care characteristics were very similar between the two groups. In particular, there were no statistical differences in age, gender, ICU occurrence, and ICU admission rates between the cohorts. The distribution of site of infection was statistically different but clinically very similar.

Incidence. Of the 6,621,559 hospitalizations recorded in the seven states, we identified 192,980 cases of severe sepsis. The mean age was 63.8 yrs, and 49.6%

Table 1. Comparison of validation and reference cohorts

Characteristic	Validation Cohort (n = 3,895)	Reference Cohort (n = 1,342)[a]	p Value
Study period	Jan 1995–Dec 1995	Jan 1993–Apr 1994	
Sampling frame	All patients identified at five of eight hospitals using ICD-9-CM criteria	Stratified sample of ICU patients and floor patients in whom blood cultures were drawn at eight hospitals using prospective clinical and physiologic criteria (9)	
Hospital occurrence rates per 100 discharges	2.1–4.3	1.1–3.3[b]	
ICU occurrence rate, %	11.2	10.4	.06
Male, %	53	56	.06
Age, mean, median yrs[c]	59, 62	59, 61	
Site of infection, %			
Respiratory	38.4	42.4	.01
Primary bacteremia	14.6	11.6	.01
Genitourinary	8.7	11.0	.01
Abdominal	9.3	9.9	.51
Device-related	4.9	6.1	.09
Wound/soft tissue	8.9	5.1	<.001
Central nervous system	1.1	2.4	<.001
Endocarditis	1.5	1.2	.43
Other/undetermined	12.6	10.3	.02
ICU admission rate, %	58	59	.52
ICU LOS, mean, median days[c]	15.7,7	17.7,8	

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICU, intensive care unit; LOS, length of stay.

[a]Sands et al. (9) described their cohort as having "confirmed sepsis syndrome." However, their criteria are the American College of Chest Physicians/Society of Critical Care Medicine criteria for severe sepsis (7) and consist of signs of infection plus organ failure; [b]The 95% confidence interval across sites ranged from 1.0 to 4.1; [c]We could not test for differences in age or ICU LOS because we only had the measures of central tendency and not the actual distributions of these variables for the Sands et al. cohort.

Table 2. Characteristics of study cohort (n = 192,980)

Characteristic	Occurrence, %	Mortality, %
Underlying comorbidity		
Chronic obstructive pulmonary disease	12.3	32.1
Neoplasm (nonmetastatic)	11.6	36.9
HIV disease	6.3	34.0
Chronic liver disease	4.5	37.1
Chronic renal disease	5.4	36.7
Neoplasm (metastatic)	5.3	43.4
Complicated diabetes	3.2	24.0
Peripheral vascular disease	3.1	30.9
Autoimmune disease	1.5	23.5
Any underlying comorbidity	55.5	31.8
Acute organ dysfunction		
Number of systems		
1	73.6	21.2
2	20.7	44.3
3	4.7	64.5
≥4	1.0	76.2
Organ system		
Respiratory	45.8	40.1
Cardiovascular	24.4	32.4
Renal	22.0	38.2
Hematologic	20.6	22.8
Central nervous system	9.3	24.4
Hepatic	1.3	54.3
Site of infection		
Respiratory	44.0	32.9
Bacteremia, site unspecified	17.3	41.2
Genitourinary	9.1	16.1
Abdominal	8.6	19.5
Wound/soft tissue	6.6	20.6
Device-related	2.2	18.1
Central nervous system	0.8	29.5
Endocarditis	0.6	33.1
Other/unspecified	10.8	15.4
ICU admission	51.1	34.1
Medical condition	71.4	29.2
Surgical condition	28.6	26.2

HIV, human immunodeficiency virus; ICU, intensive care unit.

were male. Descriptive characteristics are provided in Table 2. After we adjusted for age and gender, the national incidence rate was 3.0 cases per 1,000 population (2.26 cases per 100 hospital discharges). This produced a national estimate of 751,000 cases per annum, of which 416,700 (55.5%) had underlying comorbidity and 160,700 (21.4%) were surgical. Overall, 383,000 (51.1%) received ICU care. An additional 84,000 (11.1%) received care in a coronary care unit, and 46,000 (6.2%) were ventilated in an intermediate care unit but never received ICU care.

The number of cases and incidence rates by age are shown in Figure 1. The incidence was high in infants (5.3/1,000 aged <1 yr), decreased quickly in older children (0.2/1,000 aged 5–14 yrs), increased slowly through most of adulthood (5.3/1,000 aged 60–64 yrs), and increased sharply in the elderly (26.2/1,000 aged ≥85 yrs). The number of cases also increased with age, although the peak

was earlier, such that more than half of patients were ≥65 yrs (437,400, 58.3%) and more than one third were ≥5 yrs (274,000, 36.6%). There was also a "bump" in the number of young adults attributable to patients with HIV-related conditions (n = 47,200, average age 38.5 yrs).

Excluding patients with HIV disease, the overall incidence rate for women was similar to that of men (2.87 vs. 2.83 cases per 1,000 population). However, the age-specific incidence rate was lower in women than in men such that, from age 30 onward, women had a rate similar to that of men 5 yrs younger (Fig. 2). Women were more likely to have genitourinary infections (11.8 vs. 6.3%, $p <$ .0001) and less likely to have respiratory infections (39.9 vs. 48.1%, $p <$ .0001) but otherwise had a similar distribution of sites of infection.

Mortality. The overall hospital mortality rate was 28.6%, which represents 215,000 deaths nationally. Mortality rates

were higher for patients with preexisting disease, medical conditions, ICU care, and more organ failure (Table 2). Mortality increased with age from 10% in children to 38.4% in those ≥85 yrs (Fig. 3). This trend was most obvious in those without underlying comorbidity. For patients with underlying comorbidity, mortality was much higher and changed little throughout most of adulthood.

There was no gender difference in mortality in children, but the mortality rate for men was slightly higher than for women (29.3 vs. 27.9%, $p <$ .0001). The widest difference (20.9 vs. 13.9%, $p <$ .0001) occurred in those 25–30 yrs of age, but the effect was observed throughout adulthood. Excluding HIV cases, mortality rates for women aged ≥30 yrs, like the incidence rates, were similar to that of men 5 yrs younger (Fig. 2). In multivariate regression, these differences were explained by differences in age, underlying comorbidity, and site of infection. In other words, although the chances of developing sepsis differed for men and women by age, the likelihood of dying from sepsis was the same for men and women after adjusting for age, underlying comorbidity, and site of infection.

Hospital Resource Use and Costs. The average LOS and cost per case were 19.6 days and $22,100. Nonsurvivors had a similar LOS (19.9 vs. 19.4 days, $p <$ .005) but cost considerably more ($25,900 vs. $20,600, $p <$ .0001) than survivors. ICU patients stayed longer (23.3 vs. 15.6 days, $p <$ .0001) and cost more ($29,900 vs. $13,900, $p <$ .0001) than non-ICU patients, and surgical patients stayed longer (24.0 vs. 18.3 days, $p <$ .0001) and cost more ($30,800 vs. $19,700, $p <$ .0001) than medical patients. Males stayed slightly longer (19.6 vs. 19.5 days, $p <$ .0001) and cost more ($23,000 vs. $21,200, $p <$ .0001) than females. LOS varied little with the number of organ systems in which acute dysfunction developed (range, 18.5–22.8 days), but average costs increased from $19,500 for those with acute dysfunction in one system to $32,800 for those with dysfunction in four or more systems.

Average and total costs by age are shown in Figure 4. Adult costs were generally stable around $21,000–25,000, except in the oldest patients ($14,600 for those aged ≥85 yrs). Infants were the most expensive, with an average cost of $54,300, whereas the average cost for patients aged 1–19 yrs was $28,000. ICU admission rates were generally high
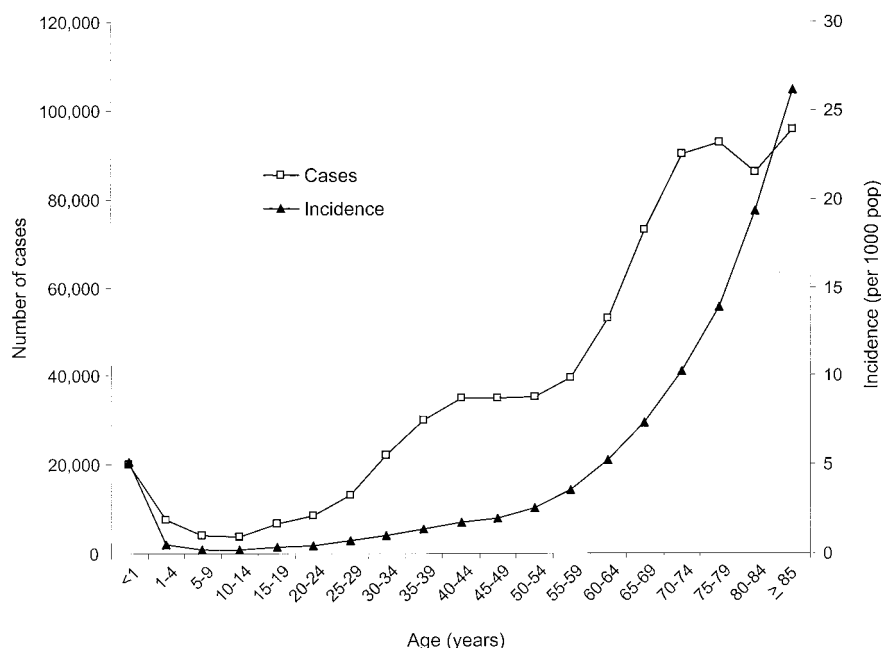
Figure 1. National age-specific number and incidence of cases of severe sepsis. National estimates are generated from the seven-state cohort using state and national age- and gender-specific population estimates from the National Center for Health Statistics and the U.S. Census. *pop*, population.
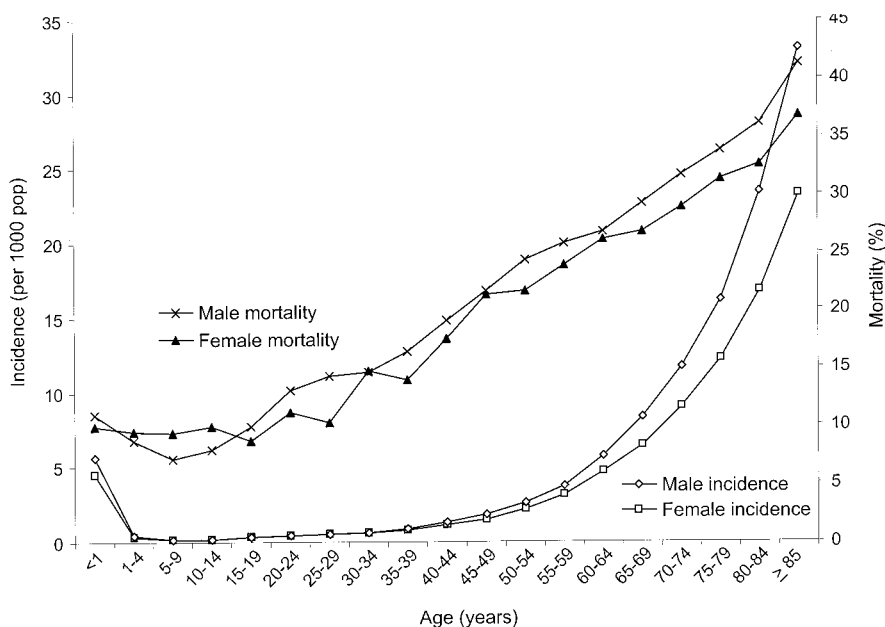

Figure 2. National age-specific incidence and mortality rates for all cases of severe sepsis by gender, excluding those with HIV disease. National estimates are generated from the seven-state cohort using state and national age-specific population estimates from the National Center for Health Statistics and the U.S. Census. The incidence among women was equivalent to that of men 5 yrs younger. A similar age-based difference was seen in mortality but, in multivariate regression, this difference was explained by underlying comorbidity and site of infection. *pop*, population.

across all ages but were highest in infants (58.2%) and lowest in adults aged 30–39 yrs (41.1%) and those aged ≥85 yrs (40%). Of note, patients with HIV disease had a much lower ICU admission rate (26.0%), partially explaining the lower ICU admission rates in those aged 30–39 yrs.

The total national hospital cost associated with the care of patients who incurred severe sepsis was $16.7 billion. The costs of care for patients aged <1 yr and 1–19 yrs were $1.1 billion and $622 million, representing 6.6% and 3.7% of the total costs. The costs of care for patients aged ≥65 and ≥75 yrs were $8.7 billion and $5.1 billion, representing 52.3% and 30.8% of the total costs.

Comparison of Teaching to Nonteaching Hospitals. There were 847 hospitals in our data set, of which 84 (9.9%) were teaching institutions. About one fourth of all cases were managed at these teaching hospitals (Table 3). Patients at teaching hospitals were younger, more likely to have HIV disease, and less likely to have chronic obstructive pulmonary disease but otherwise had similar comorbidity, ICU use, and mortality. Both costs and LOS were considerably higher at teaching hospitals. Higher costs and longer LOS also were incurred in larger hospitals when we stratified hospitals by the number of beds (data not shown).

Population-Based Projections of the Future National Occurrence of Sepsis. Assuming only the U.S. Census-projected changes in the population, we estimated the number of cases to increase steadily at 1.5% per annum, yielding 934,000 and 1,110,000 cases by the years 2010 and 2020. This increase is faster than the anticipated population growth and is attributable to the high incidence of sepsis in older patients and the disproportionate growth of the elderly in the U.S. population.

DISCUSSION

We found that severe sepsis is very common, consumes considerable healthcare resources, and is associated with a high mortality rate. The 215,000 deaths we estimated were 9.3% of all deaths in the United States in 1995 and equaled the number of deaths after acute myocardial infarction (24). Although many of the deaths after sepsis may not be caused by sepsis, the magnitude of our national estimates underscores the importance of sepsis as a major health problem.

Our overall hospital mortality rate of almost 30% was typical of most prior sepsis studies, but the rate was much lower in children and previously healthy adults. Pediatric and adult sepsis populations have not been studied together before, but a recent study of pneumococcal bacteremia also demonstrated wide variation in mortality from 3.2% in children to 43% in the elderly (25). Such variation raises the possibilities that the attribut-
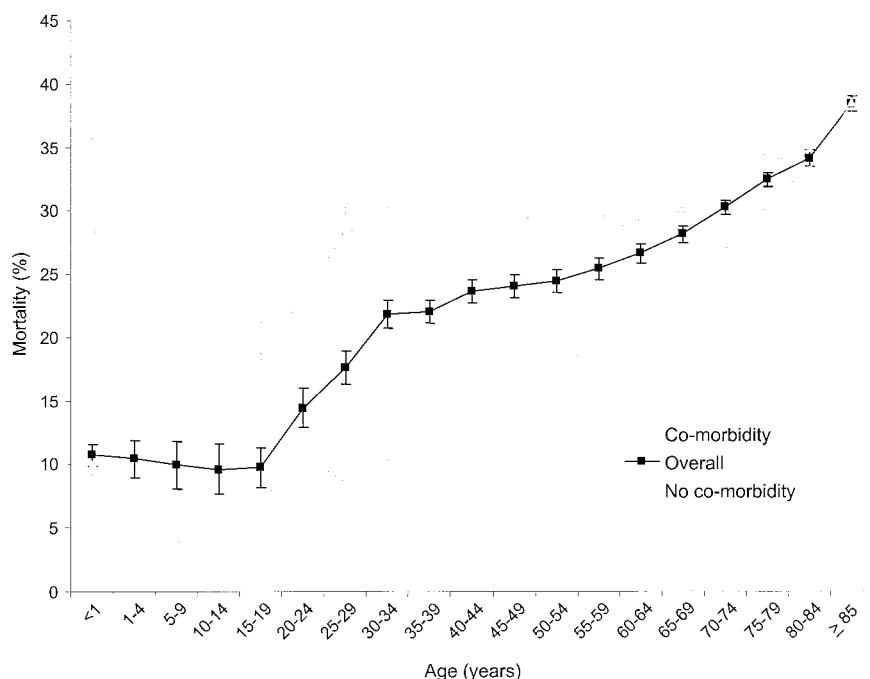
Figure 3. National age-specific mortality rates for all cases of severe sepsis and for those with and without underlying comorbidity. Comorbidity is defined as a Charlson-Deyo score (23) >0. National estimates are generated from the seven-state cohort using state and national age- and gender-specific population estimates from the National Center for Health Statistics and the U.S. Census. Error bars represent 95% confidence intervals.
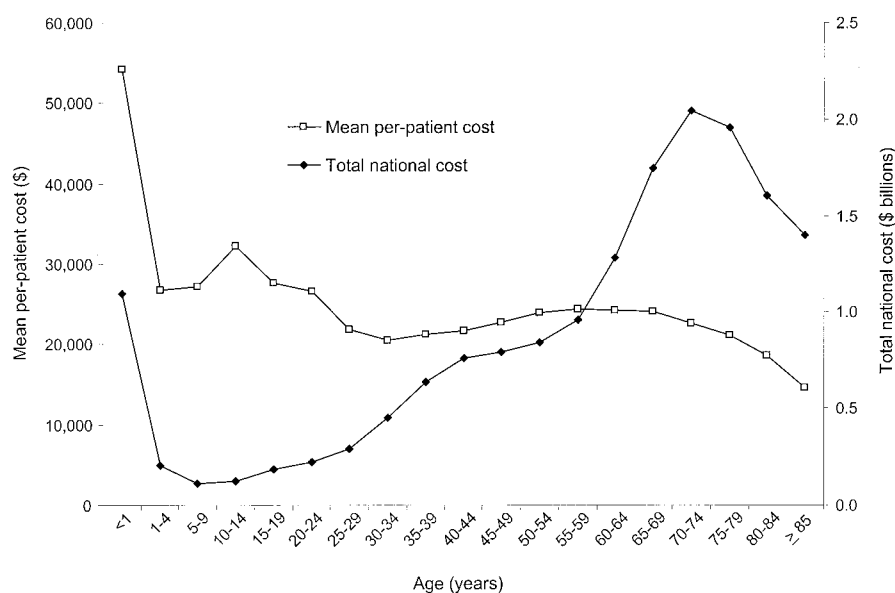

Figure 4. National age-specific average and total hospital costs for severe sepsis. Costs are calculated by multiplying total hospital charges by the hospital-specific cost-to-charge ratio derived from the Health Care Financing Administration Provider Specific File (19). All costs are expressed as 1995 U.S. dollars. National estimates are generated from the seven-state cohort using state and national age- and gender-specific population estimates from the National Center for Health Statistics and the U.S. Census.

able mortality of sepsis may be much less than the commonly observed 30% and that the mechanism by which sepsis causes death is highly dependent on individual patient factors, many of which may not be reversible by single antisepsis agents. This potential for an attributable mortality much lower than 30% supports the argument that many recent trials of antisepsis agents were underpowered, designed only to find unrealistically large effect sizes (26).

Clinical trials of antisepsis agents often exclude the very elderly, patients with HIV disease, and patients with malignancy. This is because these patients are believed to be at higher risk of death, as confirmed by our data, and less likely to respond to treatment. The conventional wisdom also may have been that such patients are rare. However, we found that these patients are a large proportion of the sepsis population, and their exclusion will compromise the external validity, or representativeness, of these trials. Because new antisepsis therapies may well be expensive to use (27), a full understanding of their effectiveness and cost-effectiveness in different patient populations is essential.

Beyond the implications for clinical trials, our observation that sepsis is a disease of the elderly also mandates consideration of the appropriateness of care, including determination of patient preferences. Our data suggest that there are already differences in the aggressiveness of treatment in this group, with lower length of stay, ICU use, and hospital costs in those aged >85 yrs. Yet, aggressive care is not futile in the elderly, and the majority survive to hospital discharge. Unfortunately, there are limited data on the subsequent survival (28) or quality of life (29) after sepsis, especially in the elderly. Such information will be crucial in determining optimal healthcare policy as the U.S. population ages and the number of cases of sepsis increases. There also may be other important trends over time. The large proportion of cases related to HIV may change over time. There is hope that the incidence of HIV infection will continue to decrease, but, with new therapies prolonging survival, prevalence will likely increase. Forecasting the consequences for severe sepsis will be difficult, and we recommend continued follow-up.

Several recent studies have suggested that gender, perhaps through differences in sex hormones (30–32), may be an important risk factor for adverse outcome in infection and sepsis. However, some studies found that women fared better (30, 31) whereas others found the opposite (32). We found that women did have lower age-adjusted severe sepsis rates, mainly attributable to fewer episodes of respiratory origin. We do not know, however, whether this represents a difference in the distribution of risk factors, such as chronic obstructive pulmonary disease, or a difference in access to care. We also found that mortality was lower in women

Table 3. Comparison of teaching[a] to nonteaching hospitals

Characteristic	Teaching[b]	Nonteaching
n (% of total)	53,089 (27.5)	139,891 (72.5)
Age, mean, median yrs	57.0, 63	66.5, 72
Gender, % male	51.9	48.8
Average number of organ systems with acute dysfunction	1.35	1.33
Comorbidity		
Charlson-Deyo index >0, %	55.0	55.7
Chronic obstructive pulmonary disease, %	7.8	13.9
HIV disease, %	10.1	4.9
Resource use		
Hospital LOS, mean ± SD, median	24.1 ± 33.4, 15	17.6 ± 32.4, 11
Hospital cost, mean ± SD, median U.S. $1,000	30.6 ± 40.7, 17.3	18.4 ± 27.7, 10.4
ICU admission rate, %	51.8	50.8
ICU LOS, mean ± SD, median	13.8 ± 20.0, 7	10.0 ± 13.8, 6
Hospital LOS for ICU patients, mean ± SD, median	28 ± 36.9, 19	20.8 ± 34.4, 14
Hospital cost for ICU patients, mean ± SD, median U.S. $1,000	42.1 ± 47.1, 27.6	24.6 ± 31.3, 15.7
Hospital mortality, %	29.7	28.1

HIV, human immunodeficiency virus; LOS, length of stay; ICU, intensive care unit.

[a]Teaching defined as member of the Council of Teaching Hospitals, derived from the American Hospital Association 1995 Guide to the Health Care Field (20); [b]All variables were statistically significantly different between teaching and nonteaching hospitals ($p < .0001$) with the exception of the Charlson-Deyo index >0.

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but that this was explained by differences in age, comorbidity, and site of infection. The gender differences we observed were consistent throughout adulthood, with no obvious link to menopause, suggesting that the differences are not solely mediated through sex hormones. Thus, we recommend that future research on gender differences in sepsis focus on understanding the processes that lead to the site and type of infection and on understanding whether there are systematic differences in healthcare access and delivery.

There is limited information on the hospital costs and resource use associated with the care of septic patients. Chalfin et al. (33) analyzed 1,405 patients at a teaching hospital and estimated mean total charges of $38,304 in survivors and $49,182 in nonsurvivors. When we adjust for inflation and use an average cost-to-charge ratio, these estimates are consistent with our findings for costs at teaching hospitals. Costs of care appear lower at nonteaching hospitals, attributable presumably to differences in case-mix, differences in care, such as the costs of teaching, or both. Perhaps contrary to clinical intuition, we found that many patients with sepsis did not receive ICU care. This observation was also made by others (8, 9). Whether such patients would have benefited from ICU care is unclear, and it is possible that the ACCP/

SCCM definition for severe sepsis, intended for ICU patients, selects different types of patients on the hospital floor.

The major limitations of our study relate to the use of administrative data to define sepsis. We selected states from the West, Northeast, Midatlantic, and Southeast regions. Although these regions represent the most heavily populated areas of the United States, we did not have representation from the Midwest or Southwest. Unfortunately, there are no statewide hospital databases from these regions with the appropriate level of detail and quality for this study. However, when generating national estimates, we adjusted for differences in population distribution between the seven-state cohort and the entire country, and we do not anticipate that additional data from the Midwest or Southwest would have altered any of our national estimates substantially. We used data from 1995, the last full year for which data were available from all seven states when we began the study. There have been no significant changes in the management of sepsis since that time, and therefore, other than the 1.5% annual increase in incidence with the aging of the population, we believe our estimates reflect current practice.

We could only identify sepsis by using ICD-9-CM codes, rather than clinical and physiologic measurements. The data set

was not designed primarily for research and consequently did not necessarily have the same level of data auditing and quality that might be expected in a prospective study. Although our definition combined infection with organ dysfunction within the same admission, the time overlap was not as tight as in clinical trials, which usually specify an overlap of infection and organ failure within a time window of 12–72 hrs, depending on the study. Our definition of severe sepsis also could be considered more inclusive than others (e.g., a patient with bacterial pneumonia would be considered to have severe sepsis if mechanical ventilation was required). Finally, both the hospital costs and mortality rates are all-cause estimates and not the attributable costs or mortality rates of sepsis. Thus, preventing sepsis altogether would only diminish, and not extinguish, these costs and deaths. At the same time, our estimates do not include costs or mortality rates after hospital discharge. There is evidence that hospital survivors of severe sepsis remain at considerably increased risk of death compared with nonseptic controls (28).

Despite these limitations, our approach captured patients similar to those identified using more rigorous prospective screening criteria. In addition to the close comparison with Sands et al. (9), our findings with regard to site of infection, ICU use, and hospital mortality are also very similar to the other U.S. study, by Rangel-Frausto et al. (8) We believe the comparison of our ICD-9-CM coding scheme to the prospective criteria was a strength of this study. However, the validity of our approach could have been verified further if the comparison cohort

included children and if detailed chart review had been possible.

In conclusion, we found that severe sepsis is a common, frequently fatal, and expensive condition. It is especially common in the elderly and is likely to increase substantially in the coming years as the U.S. population ages. Although we applaud the continued search for effective antisepsis drugs, we also encourage attention to other aspects of care. In particular, we believe that this study highlights a variety of epidemiologic and health services research issues that remain poorly understood, including optimal delivery of care for vulnerable and elderly populations.

ACKNOWLEDGMENTS

REFERENCES

1. Wheeler AP, Bernard GR: Treating patients with severe sepsis. *N Engl J Med* 1999; 340: 207–214
2. Dellinger RP: From the bench to the bedside: The future of sepsis research. Executive summary of an American College of Chest Physicians, National Institute of Allergy and Infectious Disease, and National Heart, Lung, and Blood Institute Workshop. *Chest* 1997; 111:744–753
3. Centers for Disease Control: Increase in national hospital discharge survey rates for septicemia—United States, 1979–1987. *JAMA* 1990; 263:937–938
4. Bernard GR, Wheeler AP, Russell JA, et al: The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med* 1997; 336:912–918
5. Kieft H, Hoepelman AI, Zhou W, et al: The sepsis syndrome in a Dutch university hospital. Clinical observations. *Arch Intern Med* 1993; 153:2241–2247
6. Opal SM, Fisher CJ Jr, Dhainaut JF, et al: Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial. *Crit Care Med* 1997; 25: 1115–1124
7. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
8. Rangel-Frausto MS, Pittet D, Costigan M, et al: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 1995; 273:117–123
9. Sands KE, Bates DW, Lanken PN, et al: Epidemiology of sepsis syndrome in 8 academic medical centers. Academic Medical Center Consortium Sepsis Project Working Group. *JAMA* 1997; 278:234–240
10. Hospital inpatient data file, State of Florida. State of Florida, Agency for Health Care Administration, 2000
11. Maryland acute care inpatient data. State of Maryland, St. Paul Computer Center, Inc., 2000
12. FY 1996 hospital case mix data base. The Commonwealth of Massachusetts, Executive Office of Health and Human Services, 2000
13. Discharge data UB-92 YTD tape file: State of New Jersey, Department of Health and Senior Services, 2000
14. New York State Department of Health SPARCS: "Expanded administrative releasable" data. New York, State of New York Department of Health, 2000
15. Public use file-PUF1 patient level data. State of Virginia, Virginia Health Information, 2000
16. CHARS (Comprehensive Hospital Abstract Reporting System) public data file. State of Washington, Department of Health, 2000
17. US Bureau of Census: *Population Estimates Program.* Report CB97-64. Washington, DC, US Bureau of Census, 1990
18. Ventura SJ, Martin JA, Curtin SC, et al: *Report of final natality statistics, 1995.* Report CB97-64. Washington, DC, US Department of Health and Human Services, 1997
19. Health Care Financing Administration: 1995 HCFA Provider Specific File. Washington, DC, Health Care Financing Administration, 1995
20. American Hospital Association: 2000–2001 AHA Guide to the Health Care Field. Chicago, IL, Health Forum, 2000
21. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995; 23:1638–1652
22. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996; 22:707–710
23. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45:613–619
24. National Center for Health Statistics: Deaths from 282 selected causes. Available at: http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/gmwkiii.htm. Accessed January 2001
25. Mirzanejad Y, Roman S, Talbot J, et al: Pneumococcal bacteremia in two tertiary care hospitals in Winnipeg, Canada. Pneumococcal Bacteremia Study Group. *Chest* 1996; 109:173–178
26. Angus DC, Birmingham MC, Balk RA, et al: E5 murine monoclonal anti-endotoxin antibody in Gram-negative sepsis: A multicenter randomized controlled trial and implications for future sepsis trials. *JAMA* 2000; 283: 1723–1730
27. Schulman KA, Glick HA, Rubin H, et al: Cost-effectiveness of HA-1A monoclonal antibody for Gram-negative sepsis. Economic assessment of a new therapeutic agent. *JAMA* 1991; 266:3466–3471
28. Quartin AA, Schein RM, Kett DH, et al: Magnitude and duration of the effect of sepsis on survival. *JAMA* 1997; 277:1058–1063
29. Perl TM, Dvorak L, Hwang T, et al: Long-term survival and function after suspected Gram-negative sepsis. *JAMA* 1995; 274: 338–345
30. Schroder J, Kahlke V, Staubach KH, et al: Gender differences in human sepsis. *Arch Surg* 1998; 133:1200–1205
31. Wichmann MW, Inthorn D, Andress H-J, et al: Incidence and mortality of severe sepsis in surgical intensive care patients: The influence of patient gender on disease process and outcome. *Intensive Care Med* 2000; 26: 167–172
32. Crabtree TD, Pelletier SJ, Gleason TG, et al: Gender-dependent differences in outcome after the treatment of infection in hospitalized patients. *JAMA* 1999; 282:2143–2148
33. Chalfin DB, Holbein ME, Fein AM, et al: Cost-effectiveness of monoclonal antibodies to Gram-negative endotoxin in the treatment of Gram-negative sepsis in ICU patients. *JAMA* 1993; 269:249–254

APPENDIX 1

ICD-9-CM Codes Used to Identify a Bacterial or Fungal Infection

001, Cholera; 002, Typhoid/paratyphoid fever; 003, Other salmonella infection; 004, Shigellosis; 005, Other food poisoning; 008, Intestinal infection not otherwise classified; 009, Ill-defined intestinal infection; 010, Primary tuberculosis infection; 011, Pulmonary tuberculosis; 012, Other respiratory tuberculosis; 013, Central nervous system tuberculosis; 014, Intestinal tuberculosis; 015, Tuberculosis of bone and joint; 016, Genitourinary tuberculosis; 017, Tuberculosis not otherwise classified; 018, Miliary tuberculosis; 020, Plague; 021, Tularemia; 022, Anthrax; 023, Brucellosis; 024, Glanders; 025, Melioidosis; 026, Rat-bite fever; 027, Other bacterial zoonoses; 030, Leprosy; 031, Other mycobacterial disease; 032, Diphtheria; 033, Whooping cough; 034, Streptococcal throat/scarlet fever;

035, Erysipelas; 036, Meningococcal infection; 037, Tetanus; 038, Septicemia; 039, Actinomycotic infections; 040, Other bacterial diseases; 041, Bacterial infection in other diseases not otherwise specified; 090, Congenital syphilis; 091, Early symptomatic syphilis; 092, Early syphilis latent; 093, Cardiovascular syphilis; 094, Neurosyphilis; 095, Other late symptomatic syphilis; 096, Late syphilis latent; 097, Other and unspecified syphilis; 098, Gonococcal infections; 100, Leptospirosis; 101, Vincent's angina; 102, Yaws; 103, Pinta; 104, Other spirochetal infection; 110, Dermatophytosis; 111, Dermatomycosis not otherwise classified or specified; 112, Candidiasis; 114, Coccidioidomycosis; 115, Histoplasmosis; 116, Blastomycotic infection; 117, Other mycoses; 118, Opportunistic mycoses; 320, Bacterial meningitis; 322, Meningitis, unspecified; 324, Central nervous system abscess; 325, Phlebitis of intracranial sinus; 420, Acute pericarditis; 421, Acute or subacute endocarditis; 451, Thrombophlebitis; 461, Acute sinusitis; 462, Acute pharyngitis; 463, Acute tonsillitis; 464, Acute laryngitis/tracheitis; 465, Acute upper respiratory infection of multiple sites/not otherwise specified; 481, Pneumococcal pneumonia; 482, Other bacterial pneumonia; 485, Bronchopneumonia with organism not otherwise specified; 486, Pneumonia, organism not otherwise specified; 491.21, Acute exacerbation of obstructive chronic bronchitis; 494,

Bronchiectasis; 510, Empyema; 513, Lung/mediastinum abscess; 540, Acute appendicitis; 541, Appendicitis not otherwise specified; 542, Other appendicitis; 562.01, Diverticulitis of small intestine without hemorrhage; 562.03, Diverticulitis of small intestine with hemorrhage; 562.11, Diverticulitis of colon without hemorrhage; 562.13, Diverticulitis of colon with hemorrhage; 566, Anal and rectal abscess; 567, Peritonitis; 569.5, Intestinal abscess; 569.83, Perforation of intestine; 572.0, Abscess of liver; 572.1, Portal pyemia; 575.0, Acute cholecystitis; 590, Kidney infection; 597, Urethritis/urethral syndrome; 599.0, Urinary tract infection not otherwise specified; 601, Prostatic inflammation; 614, Female pelvic inflammation disease; 615, Uterine inflammatory disease; 616, Other female genital inflammation; 681, Cellulitis, finger/toe; 682, Other cellulitis or abscess; 683, Acute lymphadenitis; 686, Other local skin infection; 711.0, Pyogenic arthritis; 730, Osteomyelitis; 790.7, Bacteremia; 996.6, Infection or inflammation of device/graft; 998.5, Postoperative infection; 999.3, Infectious complication of medical care not otherwise classified.

Where 3- or 4-digit codes are listed, all associated subcodes were included. There were 1,286 distinct infection codes in our schema. Of these, only 642 codes were detected in the sample. Among the 642 codes, 225 codes accounted for 99% of the sample and 68 codes accounted for 90%.

Appendix 2. ICD-9-CM-based classification of acute organ dysfunction

Organ System	ICD-9-CM Code Description	ICD-9-CM Code[a]
Cardiovascular	Shock without trauma	785.5
	Hypotension	458
Respiratory	Mechanical ventilation[a]	96.7
Neurologic	Encephalopathy	348.3
	Transient organic psychosis	293
	Anoxic brain damage	348.1
Hematologic	Secondary thrombocytopenia	287.4
	Thrombocytopenia, unspecified	287.5
	Other/unspecified coagulation defect	286.9
	Defibrination syndrome	286.6
Hepatic	Acute and subacute necrosis of liver	570
	Hepatic infarction	573.4
Renal	Acute renal failure	584

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.
[a]Where 3- or 4-digit codes are listed, all associated subcodes were included.