

ORIGINAL ARTICLE

The Epidemiology of Sepsis in the United States from 1979 through 2000

Greg S. Martin, M.D., David M. Mannino, M.D., Stephanie Eaton, M.D.,
and Marc Moss, M.D.

ABSTRACT

BACKGROUND

From the Division of Pulmonary, Allergy, and Critical Care, Department of Medicine, Emory University School of Medicine (G.S.M., S.E., M.M.); and the National Center for Environmental Health, Centers for Disease Control and Prevention (D.M.M.) — both in Atlanta. Address reprint requests to Dr. Martin at the Division of Pulmonary, Allergy, and Critical Care, Department of Medicine, Emory University, Grady Memorial Hospital, 69 Jesse Hill Jr. Dr., SE, Rm. 2D-004, Atlanta, GA 30303, or at greg_martin@emory.org.

Sepsis represents a substantial health care burden, and there is limited epidemiologic information about the demography of sepsis or about the temporal changes in its incidence and outcome. We investigated the epidemiology of sepsis in the United States, with specific examination of race and sex, causative organisms, the disposition of patients, and the incidence and outcome.

METHODS

We analyzed the occurrence of sepsis from 1979 through 2000 using a nationally representative sample of all nonfederal acute care hospitals in the United States. Data on new cases were obtained from hospital discharge records coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification*.

RESULTS

Review of discharge data on approximately 750 million hospitalizations in the United States over the 22-year period identified 10,319,418 cases of sepsis. Sepsis was more common among men than among women (mean annual relative risk, 1.28 [95 percent confidence interval, 1.24 to 1.32]) and among nonwhite persons than among white persons (mean annual relative risk, 1.90 [95 percent confidence interval, 1.81 to 2.00]). Between 1979 and 2000, there was an annualized increase in the incidence of sepsis of 8.7 percent, from about 164,000 cases (82.7 per 100,000 population) to nearly 660,000 cases (240.4 per 100,000 population). The rate of sepsis due to fungal organisms increased by 207 percent, with gram-positive bacteria becoming the predominant pathogens after 1987. The total in-hospital mortality rate fell from 27.8 percent during the period from 1979 through 1984 to 17.9 percent during the period from 1995 through 2000, yet the total number of deaths continued to increase. Mortality was highest among black men. Organ failure contributed cumulatively to mortality, with temporal improvements in survival among patients with fewer than three failing organs. The average length of the hospital stay decreased, and the rate of discharge to nonacute care medical facilities increased.

CONCLUSIONS

The incidence of sepsis and the number of sepsis-related deaths are increasing, although the overall mortality rate among patients with sepsis is declining. There are also disparities among races and between men and women in the incidence of sepsis. Gram-positive bacteria and fungal organisms are increasingly common causes of sepsis.

N Engl J Med 2003;348:1546-54.

Copyright © 2003 Massachusetts Medical Society.

CARE OF PATIENTS WITH SEPSIS COSTS as much as \$50,000 per patient,¹ resulting in an economic burden of nearly \$17 billion annually in the United States alone.² Sepsis is often lethal, killing 20 to 50 percent of severely affected patients.³ It is the second leading cause of death among patients in noncoronary intensive care units (ICUs)⁴ and the 10th leading cause of death overall in the United States.⁵ Furthermore, sepsis substantially reduces the quality of life of those who survive.^{6,7}

Accurate national data on sepsis may be used to establish health care policy and to allocate health care resources. It is impractical to attempt to obtain national epidemiologic estimates prospectively, and data from a limited population or a short period may be inaccurate, making national administrative data sets an essential tool for such investigations.⁸⁻¹⁰ Epidemiologic estimates are equally dependent on consistent defining criteria. By consensus, sepsis is defined as the combination of pathologic infection and physiological changes known collectively as the systemic inflammatory response syndrome.¹¹ Patients with acute organ dysfunction are considered to have severe sepsis. The usefulness of these definitions remains contentious,^{12,13} although their application allows the identification of patients in whom a response to effective therapy is possible.¹⁴

These consensus criteria have been applied in five epidemiologic surveys of sepsis.^{2,15-18} Brun-Buisson et al. and Alberti et al. focused on microbial patterns and the ICU-specific incidence of severe sepsis in Europe.^{15,16} Rangel-Frausto et al. described the natural history of the systemic inflammatory response syndrome in a single-institution cohort during a nine-month period.¹⁷ Sands et al., in a study involving a sample of inpatients from eight hospitals during a 16-month period, observed that sepsis accounted for 2.0 percent of all hospitalizations, with 59 percent of patients with sepsis requiring intensive care and accounting for 10.4 percent of admissions to the ICU.¹⁸ Angus et al. quantified severe sepsis in 1995, using state-hospital discharge records with codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) that are indicative of infection and organ dysfunction.² On the basis of the use of ICD-9-CM codes, a 1990 report from the Centers for Disease Control suggested that the incidence of sepsis was increasing.¹⁹

We undertook a study of nationally collected data in order to provide a broad characterization of sepsis for use in epidemiologic estimates, as well as to

identify specific groups with an altered propensity for sepsis.^{15,20-23} We sought to evaluate temporal changes in the incidence and outcome of sepsis in the United States from 1979 through 2000, with specific examination of race and sex, causative organisms, and outcome, including the disposition of patients at discharge and the effect of organ failure.

METHODS

DATA SOURCE

The National Center for Health Statistics has conducted the National Hospital Discharge Survey (NHDS) continuously since 1965. Since 1979, the NHDS has conformed to the guidelines of the Uniform Hospital Discharge Data Set for consistency of reporting in records. The NHDS is composed of a sample of all nonfederal acute care hospitals in the United States, including approximately 500 hospitals, with equal representation of all geographic regions. The data base is constructed through the surveying of discharge records for inpatients from each participating hospital, representing approximately 1 percent of all hospitalizations, or 350,000 discharges annually in the United States. Discharge records are abstracted for demographic information (age, sex, ethnic background, geographic location, and marital status), seven diagnostic codes (from ICD-9-CM), four procedural codes (from *Current Procedural Terminology* [CPT]), dates of hospital admission and discharge, sources of payment, and disposition at discharge.

DEFINITIONS

Cases were identified from discharge records in the NHDS that included a code for sepsis. Sepsis was defined by the presence of any of the following ICD-9-CM codes: 038 (septicemia), 020.0 (septicemic), 790.7 (bacteremia), 117.9 (disseminated fungal infection), 112.5 (disseminated candida infection), and 112.81 (disseminated fungal endocarditis). Organ failure was defined by a combination of ICD-9-CM and CPT codes, as outlined in the Appendix.

VALIDATION

The ICD-9-CM coding system for identifying patients with sepsis was validated by nested case-control analysis. The patients with sepsis were patients admitted to a large university hospital during a six-month period with a 038 code in their discharge records. The controls were patients admitted im-

mediately before or after each identified patient with sepsis, who were included if there was no 038 code in their discharge records. Sepsis was deemed to be present when the consensus-conference definition of sepsis was met.¹⁴

STATISTICAL ANALYSIS

Incidence were normalized to the population distribution in the 2000 U.S. Census, and all estimates are presented according to accepted guidelines for the accuracy of NHDS data. That is, only absolute, unweighted samples of more than 60 patients with relative standard error (RSE) measures of less than 30 percent were included in data analyses. The RSE was calculated as a first-order Taylor-series approximation with the use of SUDAAN software,²⁴ as outlined in the RSE tables of the 2000 NHDS documentation.²⁵ The standard error was calculated by multiplying the RSE by the estimated incidence or mortality rate, and 95 percent confidence intervals were calculated from these standard errors with the use of Excel software (Microsoft). Data for continuous variables were compared by analysis of variance, and data for categorical variables were compared by the chi-square test or Fisher's exact test, as appropriate for the size of the sample, with the use of SAS software (SAS Institute). Annual data are divided into four subperiods (1979 through 1984, 1985 through 1989, 1990 through 1994, and 1995 through 2000) for the assessment of temporal changes or comparison of samples of limited size. Since information on race was missing for some persons (the rate of missing data on race ranged from 1 to 20 percent for any given year), these persons were excluded from the calculations of race-specific rates but were included in all other calculations of rates. Reported P values are two-sided.

RESULTS

DEMOGRAPHICS

During the study period, there were a total of approximately 750 million hospitalizations in the United States. The demographic characteristics of and co-existing conditions in the population of patients with sepsis in each of the four subperiods are shown in Table 1. The average age of patients with sepsis increased consistently over time, from 57.4 years in the first subperiod to 60.8 years in the last subperiod (the mean change between these subperiods was an increase of 3.5 years [95 percent confidence interval, 2.1 to 4.9 years]). Sepsis developed later in

life in female patients than in male patients — the mean age among women was 62.1 years, as compared with 56.9 years among men (difference, 5.2 years [95 percent confidence interval, 4.1 to 6.0 years]). There was a similar pattern to the increases in incidence among men and among women, although the incidence among women increased more rapidly during the study period (an annualized increase of 8.7 percent vs. 8.0 percent). Although men accounted for 48.1 percent of cases of sepsis on average per year, adjustment for sex in the population of the United States reveals that in every year, men were more likely to have sepsis than women (mean annual relative risk, 1.28 [95 percent confidence interval, 1.24 to 1.32]) (Fig. 1).

Whites had the lowest rates of sepsis during the study period, with both blacks and other nonwhite groups having a similarly elevated risk as compared with whites (mean annual relative risk, 1.89 [95 percent confidence interval, 1.80 to 1.98] and 1.90 [95 percent confidence interval, 1.80 to 2.00], respectively) (Fig. 2). Black men had the highest rate of sepsis during the study period (330.9 cases per 100,000), the youngest age at onset (mean age, 47.4 years), and the highest mortality (23.3 percent).

INCIDENCE

During the 22-year study period, there were 10,319,418 reported cases of sepsis (accounting for 1.3 percent of all hospitalizations). The number of patients with sepsis per year increased from 164,072 in 1979 to 659,935 in 2000 (an increase of 13.7 percent per year). After normalization to the population distribution in the 2000 U.S. Census, the incidence of sepsis increased over the 22-year period from 82.7 cases per 100,000 population to 240.4 cases per 100,000 population, for an annualized increase of 8.7 percent. The increasing incidence was most apparent during the first two subperiods, from 1979 through 1989.

CAUSATIVE ORGANISMS

From 1979 through 1987, gram-negative bacteria were the predominant organisms causing sepsis, whereas gram-positive bacteria were reported most commonly in each subsequent year (Fig. 3). Among the organisms reported to have caused sepsis in 2000, gram-positive bacteria accounted for 52.1 percent of cases, with gram-negative bacteria accounting for 37.6 percent, polymicrobial infections for 4.7 percent, anaerobes for 1.0 percent, and fungi for 4.6 percent. Specific organisms causing sepsis

Table 1. Characteristics of Patients with Sepsis, According to Subperiod.*

Characteristic	1979–1984 (N=1,332,468)	1985–1989 (N=2,220,659)	1990–1994 (N=2,697,472)	1995–2000 (N=4,068,819)
Demographic characteristics				
Age — yr	57.4±28.9	59.3±22.9	60.8±16.2	60.8±13.7
Male sex — %	49.6	48.9	46.8	48.0
Race — no./100,000 population (% of patients)†				
White	92.1 (81.2)	166.4 (80.3)	167.8 (78.5)	186.3 (76.3)
Black	163.0 (15.2)	301.7 (16.0)	322.8 (17.2)	378.2 (17.7)
Other	187.3 (3.6)	298.0 (3.7)	300.6 (4.3)	370.5 (6.0)
Length of hospital stay — days	17.0±8.5	15.6±6.0	15.3±4.0	11.8±2.6
Coexisting conditions — % of patients				
Chronic obstructive pulmonary disease	5.7	7.3	9.3	12.1
Congestive heart failure	8.6	9.9	13.6	15.2
Cancer	17.1	17.9	18.0	14.5
HIV infection‡	—	1.0	2.1	2.0
Cirrhosis	2.4	2.5	2.2	2.3
Diabetes	12.2	14.5	16.9	18.7
Hypertension	7.0	9.2	13.6	18.6
Pregnancy	0.6	0.5	0.4	0.3
No. of organs with failure — % of patients				
0	83.2	78.1	74.0	66.4
1	13.6	17.9	20.1	24.6
2	2.7	3.5	4.8	7.1
≥3	0.5	0.5	1.1	1.9

* Plus-minus values are means ±SE. HIV denotes human immunodeficiency virus.

† Data are normalized for race in the 2000 U.S. Census.

‡ HIV-specific coding appeared in 1986.

were recorded in 51 percent of all discharge records over the 22-year period, with the rate increasing during the first subperiod and remaining static thereafter. The greatest relative changes were observed in the incidence of gram-positive infections, which increased by an average of 26.3 percent per year. The number of cases of sepsis caused by fungal organisms increased by 207 percent, from 5231 cases in 1979 to 16,042 cases in 2000.

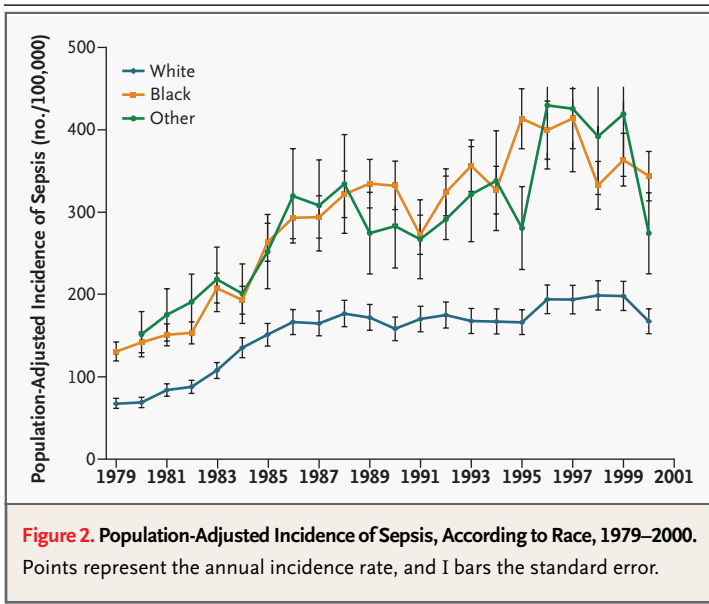
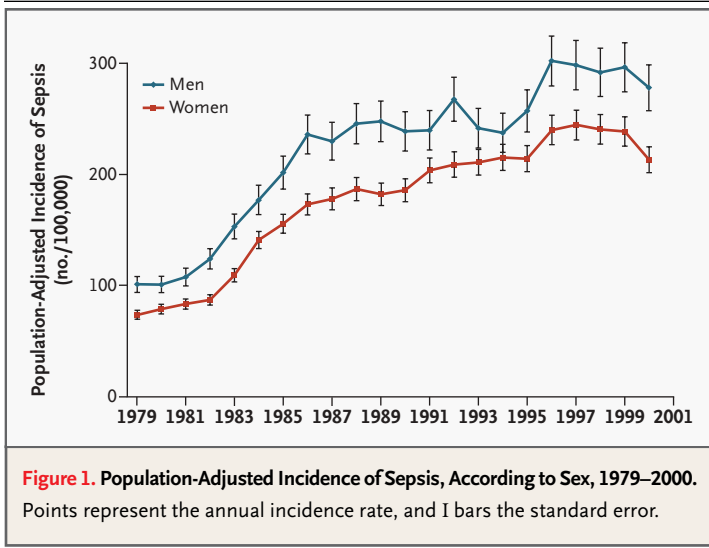
DISPOSITION OF PATIENTS

In 1979, 78.5 percent of surviving patients were discharged home; the rate decreased to 56.4 percent in 2000. Concurrently, the rate of discharge to other health care facilities (i.e., rehabilitation centers or

other long-term care facilities) increased from 16.8 percent to 31.8 percent of all survivors of sepsis-related hospitalizations (P<0.001). Over time, significantly more patients had hospitalizations of fewer than 7 days, and significantly fewer patients stayed in the hospital more than 30 days (P<0.001 for both trends).

ORGAN FAILURE AND MORTALITY

Mortality rates for the entire cohort declined over the 22-year period, averaging 27.8 percent during the first subperiod and 17.9 percent during the final subperiod (P<0.001) (Fig. 4). Despite the improved survival rates, the increasing incidence of sepsis resulted in nearly a tripling of the number of



in-hospital deaths related to sepsis, from 43,579 deaths (21.9 per 100,000 population) in 1979 to 120,491 deaths (43.9 per 100,000 population) in 2000 ($P < 0.001$). Mortality remained static for gram-positive causes of sepsis, whereas mortality related to gram-negative organisms decreased by an average of 2.9 percent per year. When stratified according to race, the mortality rate among blacks (mean, 22.8 percent for the entire study period [95 percent confidence interval, 20.5 to 25.1]) and that among whites (mean, 22.3 percent [95 percent confidence interval, 20.6 to 24.0]) were higher than that for oth-

er races (mean, 18.8 percent [95 percent confidence interval, 17.1 to 20.5 percent]). Mortality rates did not differ significantly according to sex (men, 22.0 percent; women, 21.8 percent).

The proportion of patients with sepsis who had any organ failure, a marker of the severity of illness, increased over time, from 19.1 percent in the first 11 years to 30.2 percent in later years. Organ failure occurred in 33.6 percent of patients during the most recent subperiod, resulting in the identification of 184,060 cases of severe sepsis in 1995 and 256,033 in 2000. Organ failure had a cumulative effect on mortality: approximately 15 percent of patients without organ failure died, whereas 70 percent of patients with three or more failing organs (classified as having severe sepsis and septic shock) died. The additive effect of organ failure on mortality was consistent over time, with improvements in survival being most evident among patients with fewer than three failing organs. The organs that failed most frequently in patients with sepsis were the lungs (in 18 percent of patients) and the kidneys (in 15 percent of patients); less frequent were cardiovascular failure (7 percent), hematologic failure (6 percent), metabolic failure (4 percent), and neurologic failure (2 percent).

VALIDATION

A 038 code was present in the discharge records of 72 patients during the defined cohort period. Sepsis was confirmed in 64 of these patients, yielding a positive predictive value of 88.9 percent (95 percent confidence interval, 81.6 to 96.2). The negative predictive value was 80.0 percent (95 percent confidence interval, 67.8 to 93.2). When sepsis was defined as suspected infection combined with criteria for the systemic inflammatory response syndrome and acute organ dysfunction (the accepted clinical definition), the positive predictive value of the 038 code increased to 97.7 percent (95 percent confidence interval, 93.9 to 100.0), and the negative predictive value remained at 80.0 percent.

An established combination of ICD-9-CM codes that is indicative of infection and acute organ dysfunction was applied to the NHDS data set.² The application of this combination of codes to the NHDS data base resulted in an estimate that was within 10 percent of the 751,000 cases of severe sepsis in seven states that were reported by Angus et al.² for 1995. Thus, the use of NHDS data identifies patients with sepsis with a degree of accuracy similar to that of published standards.

DISCUSSION

These data show that there are significant disparities among races and between men and women in the incidence of sepsis. There has been a substantial increase in the incidence of sepsis during the past 22 years, with an increasing number of deaths occurring despite a decline in overall in-hospital mortality.

Administrative data sets have become essential resources for epidemiologic investigations in which the prospective identification of patients is not feasible.^{8,10} Using ICD-9-CM codes, Angus et al. created a composite profile of sepsis from the 1995 hospital discharge records for seven states.² They estimated that there were 751,000 cases of severe sepsis in that year, accounting for 2.1 to 4.3 percent of hospitalizations and 11 percent of all admissions to the ICU. These estimates may overstate the incidence of severe sepsis by as much as a factor of two to four,²⁶ given that the estimated number of deaths exceeds the combined numbers of deaths reported in association with nosocomial bloodstream infections²⁷ and septic shock.²⁸

The population-adjusted incidence of sepsis in the United States has increased significantly over the past two decades. The relative frequency of specific causative organisms has shifted over time, as indicated by the published literature, with the emergence of fungal pathogens²⁹ and the recent pre-eminence of gram-positive organisms.^{20,30} The occurrence of organ failure increased over time and was an additive contributor to mortality that remained consistent among patients of different races and sexes. The decline in mortality is notable, given the expected increases associated with increasing age and the increasing severity of illness, but it is supported by previous analysis of cumulative data from clinical trials.³¹ Such changes are most likely attributable to nonspecific improvements in intensive care,^{32,33} but diagnostic criteria and coding practices may influence changes as well. The increasing rate of discharge to nonacute care medical facilities, in combination with the increasing incidence of sepsis and the decrease in overall mortality among patients with sepsis, suggests that the growing need for such care is becoming an important public health issue.

Demographic differences in the incidence and outcome of sepsis were consistent throughout the 22-year study period. Despite a predominance of women in the population of the United States and

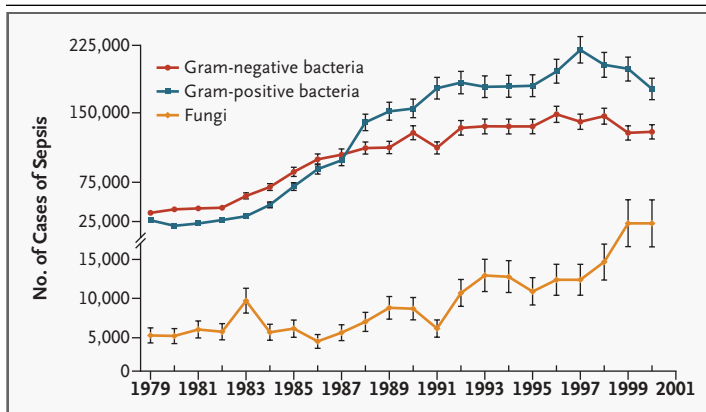


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.

Points represent the number of cases for the given year, and I bars the standard error.

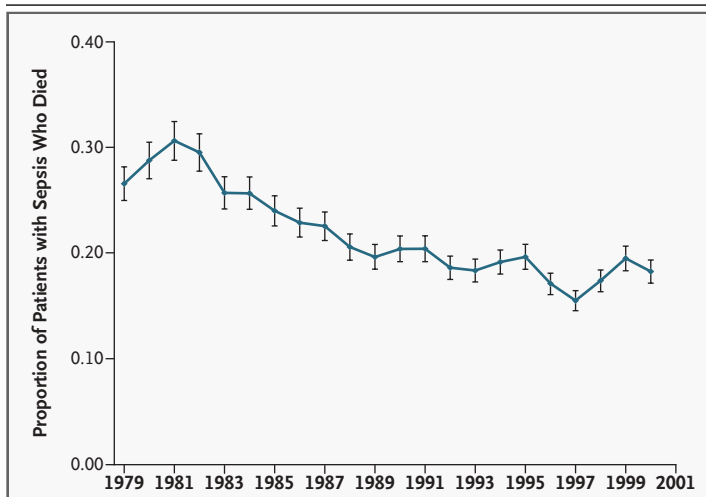


Figure 4. Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979–2000.

Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The I bars represent the standard error.

the fact that the greatest increase in incidence occurred among women, men are consistently more likely to have sepsis and are more frequently enrolled in clinical trials.^{14,34,35} The apparent racial disparities are even more striking, approaching a doubling of the risk for sepsis among nonwhites. Most prominent is the risk among black men, the group in which sepsis occurs at the youngest age and results

in the most deaths. Racial disparities in medical care and mortality have been identified previously with the use of administrative data bases,³⁶ including disparities in mortality related to infection.³⁷ Potential mechanisms for heterogeneous susceptibility to sepsis include genetic differences, which have been explored according to sex³⁸ but not according to race,³⁹⁻⁴¹ and other social and clinical factors. The underlying reasons for and the pathophysiological features of such disparities in the incidence of sepsis require further investigation.

Previous reports have suggested that the incidence of sepsis is increasing,¹⁹ and sepsis is now among the 10 leading causes of death in the United States.⁵ The finding of a large increase during the first subperiod we studied may be accurate, although other explanations are also plausible. As sepsis has become more familiar, it may have been more commonly recognized or more readily coded into medical records, and systematic shifts in the coding used in hospital discharge records may have occurred in the 1980s as hospitals tried to improve their rates of reimbursement.^{42,43} Possible reasons for a real increase in the incidence of sepsis include the increased use of invasive procedures and immunosuppressive drugs, chemotherapy, and transplantation; the emergence of the epidemic of human immunodeficiency virus (HIV) infection; and increasing microbial resistance.⁴ Although statistics related to incidence and mortality may be inexact, changes in coding would be unlikely to affect the results regarding race and sex.

Our data are limited by the quality of the NHDS data base. The advantages of a large sample size are partially offset by our inability to audit the data. There may be inherent inaccuracies, such as the attribution of death to sepsis on the basis of crude mortality data, rather than data on directly attributed mortality. NHDS data do not include important outcomes after hospitalization, and data on the disposition of patients at discharge may be influenced by the overall increase in the use of long-term care facilities. However, the demographic characteristics of this cohort of patients with sepsis are similar to those that have been identified in prospective clinical trials,^{14,34,35} and organ failure has the expected direct and additive contribution to mortality.

The coexisting conditions represented in our data are probably more representative of those in all patients with sepsis than are the conditions documented in participants in clinical trials, from which patients with certain medical conditions (e.g., cancer, HIV infection, or pregnancy) may be excluded.

The accuracy of ICD-9-CM coding for the identification of specific medical conditions remains controversial. Our validation step demonstrated that the 038 code carries a positive predictive value of 88.9 percent for the identification of true cases of sepsis.⁴⁴ Adjunctive clinical-trial data conferred a sensitivity of 87.7 percent to the 038 code.⁴⁵ If a conservative estimate of 2 percent is used for the prevalence of sepsis in hospitals in the United States,^{2,18} the specificity and negative predictive value of the 038 code may be calculated as 98.8 percent and 98.6 percent, respectively. Therefore, our coding scheme for sepsis is accurate but may, if anything, underestimate the true incidence of clinical sepsis.

Accurate national estimates regarding the epidemiology of sepsis are important for the allocation of health care resources, for the evaluation of health care delivery, and for research budgets. Temporal data may enable us to detect important trends and to track the effectiveness of care. These data provide key information about an increasingly common medical condition and have two important implications. First, the reasons underlying disparities among races and between men and women in the incidence of sepsis must be addressed. Second, further investigation is required to confirm the changes in incidence and mortality in order to project future events. Angus et al.² projected an increase in the rate of sepsis of 1.5 percent per year on the basis of the growth and aging of the U.S. population. Although their point estimates may have resulted in an overestimate of the incidence of severe sepsis in 1995, this projection represents a substantial underestimate of credible future growth according to our data. If our findings are confirmed, it will be possible to conduct an annual examination of reliable data from an existing national data set collected prospectively in the United States.

Supported by grants (HL K23-67739 to Dr. Martin and AA R01-11660 to Dr. Moss) from the National Institutes of Health.

Appendix. ICD-9-CM– or CPT-Based Classification of Acute Organ Dysfunction Associated with Sepsis.*	
Type of Organ Failure and Code	Description
Respiratory	
518.81	Acute respiratory failure
518.82	Acute respiratory distress syndrome
518.85	Acute respiratory distress syndrome after shock or trauma
786.09	Respiratory insufficiency
799.1	Respiratory arrest
96.7	Ventilator management
Cardiovascular	
458.0	Hypotension, postural
785.5	Shock
785.51	Shock, cardiogenic
785.59	Shock, circulatory or septic
458.0	Hypotension, postural
458.8	Hypotension, specified type, not elsewhere classified
458.9	Hypotension, arterial, constitutional
796.3	Hypotension, transient
Renal	
584	Acute renal failure
580	Acute glomerulonephritis
585	Renal shutdown, unspecified
39.95	Hemodialysis
Hepatic	
570	Acute hepatic failure or necrosis
572.2	Hepatic encephalopathy
573.3	Hepatitis, septic or unspecified
Hematologic	
286.2	Disseminated intravascular coagulation
286.6	Purpura fulminans
286.9	Coagulopathy
287.3-5	Thrombocytopenia, primary, secondary, or unspecified
Metabolic	
276.2	Acidosis, metabolic or lactic
Neurologic	
293	Transient organic psychosis
348.1	Anoxic brain injury
348.3	Encephalopathy, acute
780.01	Coma
780.09	Altered consciousness, unspecified
89.14	Electroencephalography

* ICD-9-CM denotes *International Classification of Diseases, Ninth Revision, Clinical Modification*, and CPT *Current Procedural Terminology*.

REFERENCES

1. Chalfin DB, Holbein ME, Fein AM, Carlson GC. Cost-effectiveness of monoclonal antibodies to gram-negative endotoxin in the treatment of gram-negative sepsis in ICU patients. *JAMA* 1993;269:249-54.
2. 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;29:1303-10.
3. Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med* 1999;340:207-14.
4. Parrillo JE, Parker MM, Natanson C, et al. Septic shock in humans: advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med* 1990;113:227-42.
5. Hoyert DL, Arias E, Smith BL, Murphy SL, Kochanek KD. Deaths: final data for 1999. National vital statistics reports. Vol. 49. No. 8. Hyattsville, Md.: National Center for Health Statistics, 2001. (DHHS publication no. (PHS) 2001-1120 PRS 01-0573.)
6. Perl TM, Dvorak L, Hwang T, Wenzel RP. Long-term survival and function after suspected gram-negative sepsis. *JAMA* 1995;274:338-45.
7. Heyland DK, Hopman W, Coe H, Tramer J, McColl MA. Long-term health-related quality of life in survivors of sepsis: Short Form-36: a valid and reliable measure of health-related quality of life. *Crit Care Med* 2000;28:3599-605.
8. Adams WL, Yuan Z, Barboriak JJ, Rimm AA. Alcohol-related hospitalizations of elderly people: prevalence and geographic variation in the United States. *JAMA* 1993;270:1222-5. [Erratum, *JAMA* 1993;270:2055.]
9. Rubenfeld GD, Angus DC, Pinsky MR, Curtis JR, Connors AF Jr, Bernard GR. Outcomes research in critical care: results of the American Thoracic Society Critical Care Assembly Workshop on Outcomes Research. *Am J Respir Crit Care Med* 1999;160:358-67.
10. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745-50.
11. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644-55.
12. Vincent JL. Dear SIRS, I'm sorry to say that I don't like you. . . . *Crit Care Med* 1997;25:372-4.
13. Abraham E, Matthay MA, Dinarello CA, et al. Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. *Crit Care Med* 2000;28:232-5.
14. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.
15. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units. *JAMA* 1995;274:968-74.
16. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002;28:108-21. [Erratum, *Intensive Care Med* 2002;28:525-6.]
17. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. *JAMA* 1995;273:117-23.
18. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 1997;278:234-40.
19. Increase in National Hospital Discharge Survey rates for septicemia — United States, 1979–1987. *MMWR Morb Mortal Wkly Rep* 1990;39:31-4.
20. Kieft H, Hoepelman AI, Zhou W, Rozenberg-Arska M, Struyvenberg A, Verhoef J. The sepsis syndrome in a Dutch university hospital: clinical observations. *Arch Intern Med* 1993;153:2241-7.
21. Salvo I, de Cian W, Musiccio M, et al. The Italian SEPSIS study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. *Intensive Care Med* 1995;21:Suppl 2:S244-S249.
22. Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. *Intensive Care Med* 1995;21:302-9.
23. Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Intensive Care Med* 2000;26:Suppl 1:S64-S74.
24. Bieler GS, Williams RL. Analyzing survey data using SUDAAN release 7.5. Research Triangle Park, N.C.: Research Triangle Institute, 1997.
25. National Hospital Discharge Survey description. Hyattsville, Md.: National Center for Health Statistics, 2002. (Accessed March 25, 2003, at <http://www.cdc.gov/nchs/about/major/hdasd/nhdsdes.htm>.)
26. Wenzel RP, Edmond MB. Severe sepsis — national estimates. *Crit Care Med* 2001;29:1472-4.
27. *Idem*. The impact of hospital-acquired bloodstream infections. *Emerg Infect Dis* 2001;7:174-7.
28. *Idem*. Managing antibiotic resistance. *N Engl J Med* 2000;343:1961-3.
29. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990: National Nosocomial Infections Surveillance System. *J Infect Dis* 1993;167:1247-51.
30. Bone RC. Toward an epidemiology and natural history of SIRS (systemic inflammatory response syndrome). *JAMA* 1992;268:3452-5.
31. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time. *Crit Care Med* 1998;26:2078-86.
32. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. *JAMA* 1995;273:306-9.
33. Abel SJ, Finney SJ, Brett SJ, Keogh BF, Morgan CJ, Evans TW. Reduced mortality in association with the acute respiratory distress syndrome (ARDS). *Thorax* 1998;53:292-4.
34. Angus DC, Birmingham MC, Balk RA, et al. E5 murine monoclonal antiendotoxin antibody in gram-negative sepsis: a randomized controlled trial. *JAMA* 2000;283:1723-30.
35. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001;286:1869-78. [Erratum, *JAMA* 2002;287:192.]
36. Whittle J, Conigliaro J, Good CB, Lofgren RP. Racial differences in the use of invasive cardiovascular procedures in the Department of Veterans Affairs medical system. *N Engl J Med* 1993;329:621-7.
37. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. *N Engl J Med* 2002;347:1585-92.
38. Hubacek JA, Stuber F, Frohlich D, et al. Gene variants of the bactericidal/permeability increasing protein and lipopolysaccharide binding protein in sepsis patients: gender-specific genetic predisposition to sepsis. *Crit Care Med* 2001;29:557-61.
39. Stuber F, Petersen M, Bokelmann F, Schade U. A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. *Crit Care Med* 1996;24:381-4.
40. Mira JP, Cariou A, Grall F, et al. Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. *JAMA* 1999;282:561-8.
41. Fang XM, Schroder S, Hoefl A, Stuber F. Comparison of two polymorphisms of the interleukin-1 gene family: interleukin-1 receptor antagonist polymorphism contributes to susceptibility to severe sepsis. *Crit Care Med* 1999;27:1330-4.
42. Hsia DC, Krushat WM, Fagan AB, Tebbutt JA, Kusserow RP. Accuracy of diagnostic coding for Medicare patients under the prospective-payment system. *N Engl J Med* 1988;318:352-5. [Erratum, *N Engl J Med* 1990;322:1540.]
43. Iezzoni LI. Assessing quality using administrative data. *Ann Intern Med* 1997;127:666-74.
44. Eaton S, Burnham E, Martin GS, Moss M. The ICD-9 code for septicemia maintains a high positive predictive value for clinical sepsis. *Am J Respir Crit Care Med* 2002;165:A471. abstract.
45. Ollendorf DA, Fendrick AM, Massey K, Williams GR, Oster G. Is sepsis accurately coded on hospital bills? *Value Health* 2002;5:79-81.

Copyright © 2003 Massachusetts Medical Society.