Published in final edited form as:

Crit Care Med. 2006 October ; 34(10): 2576–2582. doi:10.1097/01.CCM.0000239114.50519.0E.

The role of infection and comorbidity: Factors that influence disparities in sepsis

Annette M. Esper, MD, Marc Moss, MD, Charmaine A. Lewis, MD, Rachel Nisbet, MD, David M. Mannino, MD, and Greg S. Martin, MD, MSc

Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Emory University, Atlanta, GA (AME, MM, CAL, RN, GSM); and the Division of Pulmonary and Critical Care, Department of Medicine, University of Kentucky, Lexington, KY (DMM)

Abstract

Objective—Large healthcare disparities exist in the incidence of sepsis based on both race and gender. We sought to determine factors that may influence the occurrence of these healthcare disparities, with respect to the source of infection, causal organisms, and chronic comorbid medical conditions.

Design—Historical cohort study.

Setting—U.S. acute care hospitals from 1979 to 2003.

Patients—Hospitalized patients with a diagnosis of sepsis were identified from the National Hospital Discharge Survey per codes of the International Statistical Classification of Diseases, Ninth Revision (ICD-9CM). Chronic comorbid medical conditions and the source and type of infection were characterized by corresponding ICD-9CM diagnoses.

Interventions—None.

Measurements and Main Results—Sepsis incidence rates are mean cases per 100,000 after age adjustment to the 2000 U.S. Census. Males and nonwhite races were confirmed at increased risk for sepsis. Both proportional source distribution and incidence rates favored respiratory sources of sepsis in males (36% vs. 29%, $p < .01$) and genitourinary sources in females (35% vs. 27%, $p < .01$). Incidence rates for all common sources of sepsis were greater in nonwhite races, but proportional source distribution was approximately equal. After stratification by the source of infection, males (proportionate ratio 1.16, 95% confidence interval 1.04–1.29) and black persons (proportionate ratio 1.25, 95% confidence interval 1.18–1.32) remained more likely to have Gram-positive infections. Chronic comorbid conditions that alter immune function (chronic renal failure, diabetes mellitus, HIV, alcohol abuse) were more common in nonwhite sepsis patients, and cumulative comorbidities were associated with greater acute organ dysfunction. Compared with white sepsis patients, non-white sepsis patients had longer hospital length of stay (2.0 days, 95% confidence interval 1.9–2.1) and were less likely to be discharged to another medical facility (30% whites, 25% blacks, 18% other races). Case-fatality rates were not significantly different across racial and gender groups.

Conclusions—Healthcare disparities exist in the incidence of sepsis within all major sources of infection, and males and blacks have greater frequency of Gram-positive infections independent of the infection source. The differential distribution of specific chronic comorbid medical conditions

may contribute to these disparities. Large cohort and administrative studies are required to confirm discrete root causes of sepsis disparities.

Keywords

sepsis; healthcare disparities; comorbidities; infection

Sepsis is a common and lethal condition regarding which significant healthcare disparities have been reported to exist (1,2). Previous data have shown that men are 30% more likely to develop sepsis compared with women (relative risk [RR] 1.28, 95% confidence interval [CI] 1.24–1.32) (2). The male predominance in sepsis has been observed in other epidemiologic studies (3–8) as well as in randomized controlled trials (9–13). Even greater differences in the risk for sepsis exist among African Americans, where incidence rates are twice as high compared with Caucasians (RR 1.90, 95% CI 1.81–2.00). Both racial and gender disparities have been found to also exist in the pediatric sepsis population (14–16), yet the reasons for these disparities remain to be determined.

A limited number of factors have been identified that could explain the racial and gender disparities in the incidence of sepsis. Certain sources of infection are more likely to cause sepsis (1, 4, 17), and thus disproportionate source distribution may contribute to disparities in sepsis incidence. Similarly, certain types of organisms are more likely to result in sepsis or the development of acute organ dysfunction, making their distribution relevant as potential causes of sepsis disparities (18, 19). Chronic comorbid medical conditions are present in 54–65% of all sepsis patients (2, 6, 20) and strongly influence outcomes among both acutely ill patients (21) and patients with sepsis (22). The ability of chronic comorbid medical conditions to influence the risk for sepsis is not understood. Certain diseases have been suggested to increase the risk for developing sepsis, including diabetes, chronic liver disease, HIV, and cancer (5, 6). However, these factors do not explain the magnitude of difference in sepsis based on race or gender, nor do they by themselves represent true disparities in sepsis incidence.

The underlying reasons for the sepsis disparities among races and between genders have not been addressed. The identification and elimination of disparities have been espoused by physicians and by Presidential Commission, and they are a stated goal of the National Institutes of Health (23–25). Therefore, we sought to determine patient- and disease-specific variables that account for the racial and gender disparities in the incidence of sepsis. Specifically, in this study we examined the role of chronic comorbid medical conditions, the source of infection, and the type of infection as it relates to racial and gender differences in the incidence of sepsis.

METHODS

Dataset

The National Center for Health Statistics has conducted the National Hospital Discharge Survey (NHDS) continuously since 1965 (26). 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 about 500 hospitals. Discharge records from inpatients are surveyed from each hospital, representing approximately 1% of all hospitalizations in the United States. The database includes patient-specific information such as age, gender, self-reported racial category, seven diagnostic and four procedural codes (from the Clinical Modification of the International Statistical Classification of Diseases, Ninth Revision; ICD-9CM), sources of payment, and discharge disposition. This project was exempt from the

requirement for informed consent according to federal regulations of human subjects protection 45 CFR §46.101(b).

Identification of Cases

Cases were identified from discharge records in the NHDS during the 25-yr period from 1979 through 2003 that included an ICD-9CM code for sepsis as previously validated (2, 27): 038.x (septicemia), 790.7 (bacteremia), 117.9 (disseminated fungal infection), 112.5 (systemic candidiasis), and 112.81 (disseminated fungal endocarditis). Type of infection refers to the causative organism for sepsis; source of infection refers to the anatomical site of infection. The ICD-9CM codes used to classify sources of infection, comorbid medical conditions, and acute organ dysfunction are outlined in the Appendix and as previously used (2). Chronic comorbid medical conditions were also cumulatively quantified by an established comorbidity index (Charlson-Deyo score) (28–30).

Data Presentation and Statistical Analysis

Frequency counts of sepsis cases were categorized according to race and gender, and then incidence rates were calculated from the year-specific census data after age-adjusting to the distribution of the 2000 U.S. census. Information regarding the total U.S. population and racial/ethnic, gender, and age subgroups was taken from the U.S. Census Bureau 1980–2003 data files (31). Comparative census information for 1979 was linearly extrapolated from the subsequent 24 yrs. Estimates are presented according to accepted guidelines for accuracy of NHDS data, requiring absolute unweighted samples sizes >60 with relative standard error measures <30% to be included for data analysis. The relative standard error was calculated as a first-order Taylor-series approximation, as outlined in the relative standard error tables of the 2000 NHDS documentation (26). Standard error was calculated by multiplying the relative standard error by the estimate, and 95% CIs were constructed from these standard error measures. When race was missing from the sample for a given year (1–20% in any given year), these persons were excluded from the race-specific rate calculations but were included in all other rate calculations. Continuous data were compared by analysis of variance, and categorical data were compared using the chi-square test. Tests of trend within categorical variables were conducted using the Cochran-Armitage test. Analyses were performed using SAS System version 9.1 (SAS Institute, Cary, NC) (32). Differences were considered significant when the 95% CIs did not overlap or when two-sided *p* values were < .05.

RESULTS

Demographics

During the current 25-yr study period, there were approximately 930 million hospitalizations in the United States and 12,505,082 reported cases of sepsis. The demographic characteristics of the patients in the population with sepsis are shown in Table 1. When normalized to the 2000 U.S. Census, the incidence of sepsis increased over 25 yrs from 82.7 cases per 100,000 people (95% CI 71.8–93.6) in the U.S. population to 275.4 cases per 100,000 (95% CI 244.9–305.9). Consistent with previous data, males were more likely to develop sepsis than females (average annual RR 1.27, 95% CI 1.24–1.30), and blacks and other races were more likely to develop sepsis than whites (average annual black RR 1.90, 95% CI 1.82–1.98; average annual other race RR 1.85, 95% CI 1.75–1.95).

Source and Type of Infection

During the study period, 33% of sepsis cases were due to respiratory infections, 32% to genitourinary infections, 23% to a gastrointestinal source, 7% to a bone or joint infection,

5% to a skin or soft tissue infection, and 3% to other sources; 3% of infections involved more than one source. Males were more likely to have respiratory infections than women (36% vs. 29%, $p < 0.01$), whereas females more commonly developed sepsis from genitourinary sources (35% vs. 27%, $p < .01$). These differences were apparent for both population-adjusted rates (Fig. 1A) and for proportional case distribution (Fig. 1B). Fifty-two percent of sepsis patients had a microbiologically documented type of infection. Gram-positive bacteria were more common in men than in women (56% vs. 49% of cases, $p < .01$), and these differences in the type of infection were not accounted for by differences in the source of infection. After we controlled for infection source by stratification, males were 16% more likely to have Gram-positive bacterial types of infections within the most common infection sources (mean proportionate ratio 1.16, 95% CI 1.04–1.29) (Fig. 2).

Source-specific sepsis incidence rates were universally higher in nonwhite races (Fig. 3A), but these differences did not reflect increased risk for specific infection sources as racially stratified case proportions were equally distributed according to the infection site (Fig. 3B). However, black sepsis patients had the highest frequency of Gram-positive infections causing sepsis at 59% vs. 51% for whites and 48% for other races ($p < .01$ for blacks vs. either other race). These differences in the type of infection were not accounted for by the source of infection, as black sepsis patients were 25% more likely to have Gram-positive bacterial types of infections within the most common infection subtypes (mean proportionate ratio 1.25, 95% CI, 1.18–1.32) (Fig. 4).

Comorbid Conditions

The mean number of chronic comorbid medical conditions was similar for sepsis patients regardless of race or gender (Table 1). The presence of any comorbidity was more common in whites, as measured by a Charlson-Deyo comorbidity score >0 (59% in whites, 56% in blacks, 54% in other races; $p < .05$ for whites compared with blacks or others), but the severity of comorbidity as measured by total Charlson-Deyo score was greater in blacks and males (Table 1). Qualitative differences in the distribution of individual chronic comorbid medical conditions based on race and gender are apparent in Figure 5. Among racial groups (Fig. 5A), nonwhite sepsis patients had higher rates of diabetes, HIV, chronic renal failure, and alcohol abuse; white sepsis patients had higher rates of cancer and chronic obstructive pulmonary disease. There were no differences in median number of chronic comorbid medical conditions or Charlson-Deyo comorbidity score according to gender (Table 1), although chronic comorbid medical conditions were slightly more common in males than females for all conditions except diabetes mellitus (Fig. 5B).

Organ Dysfunction

Blacks and other races were more likely to have at least one acute organ dysfunction (i.e., severe sepsis) when compared with whites (35% or 37% vs. 29%, $p < .01$ compared with whites). There were smaller differences in the occurrence of organ dysfunctions between males and females (32% vs. 29%, $p = .02$). Among septic patients with chronic comorbid medical conditions, 30% of septic patients with one chronic comorbid medical condition developed acute organ dysfunction, compared with 39% of sepsis patients with two comorbid medical conditions and 45% of sepsis patients with three or more comorbidities ($p < 0.01$ for trend).

There was also a relationship between both the source of infection or the type of infection and the occurrence of acute organ dysfunction. Sepsis patients with respiratory, gastrointestinal, central nervous system, and cardiovascular infections had higher rates of acute organ dysfunction compared with other sources of infection, with the highest frequency of acute organ dysfunction (36%) observed in patients with sepsis due to

respiratory infections. In addition, sepsis patients with Gram-positive bacterial infections had a greater likelihood of developing acute organ dysfunction than those with Gram-negative infections or anaerobic or fungal sepsis (31% vs. 25% vs. 26% vs. 28%, respectively, $p < .01$ for Gram-positive compared with all others).

Clinical Outcomes

The median length of hospital stay for black sepsis patients was 1.0 day greater (95% CI 0.9–1.1 days) than for white patients and 2.0 days greater (95% CI 1.8–2.2 days) than for sepsis patients of other races (Table 1). The proportion of sepsis survivors being discharged to home after hospitalization declined from 77% in 1979 to 51% percent in 2003. Overall, nonwhites were most likely to be discharged to home after a sepsis hospitalization, whereas whites were the most frequently discharged to another medical facility (24% for whites compared with 19% for blacks and 15% for other races, $p < .05$). There were also differences in discharge status between males and females (Table 1).

Case-fatality rates were similar when stratified by gender; case fatality was lower for sepsis patients of other races (18%) compared with blacks (21%) or whites (21%) ($p < .05$) (Table 1). Fatality rates according to the source of infection were similar across racial and gender groups, with the exception of females having higher case-fatality rates for skin/soft tissue and bloodstream infections than males (13% vs. 10%, and 11% vs. 7%, respectively, both $p < .05$) and blacks having higher case-fatality rates from genitourinary sepsis than whites (17% vs. 14%, respectively, $p < .05$).

DISCUSSION

In this study using national hospitalization data, we have confirmed the frequency of sepsis and the magnitude of existing racial and gender disparities and have begun to identify factors that may influence these disparities. For the first time, we have shown that racial disparities exist within all major sources of sepsis and that gender-based disparities vary according to the source of infection. More important, there are differences in the type of infection according to race and gender that persist even within subgroups of infection sources (Gram-positive infections disproportionately represented in males and blacks). Furthermore, there were significant differences in the distribution of chronic comorbid medical conditions according to both gender and race, and the presence of comorbidities was associated with the development of acute organ dysfunction (i.e., severe sepsis). Finally, hospital length of stay and hospital discharge status were significantly different between races.

Our prior studies on the epidemiology of sepsis have documented the magnitude of racial disparities in the incidence of sepsis (2), which have also been broached by others (14, 33), yet no studies have comprehensively examined the factors that influence these disparities. Wong et al. (34) reported that differences in life-years lost due to racial disparities in infectious diseases are second only to disparities in cardiovascular diseases. As with our current data, they reported that diabetes, hypertension, and HIV contributed to the disparities among blacks. The differential distribution toward nonwhites of chronic comorbid medical conditions that affect the immune system (diabetes, chronic renal failure, and HIV) may contribute to disparities in the incidence of sepsis. In addition, these data confirm differences in causative organisms not accounted for by the site of infection, with specific increases in infections due to Gram-positive bacteria in blacks. These differences were present overall and within infection subtypes, raising questions of exposure, host susceptibility, and immune response according to racial subgroups. Racial examination of genetic predisposition is confounded in the United States by race and ethnicity, representing a social construct more than a scientific classification (35). However, the social disadvantages that

occur among the races may play a role in explaining the disparities observed in this study. However, the immunologic response to Gram-positive infections may be mediated through the human Toll-like receptor 2, and mutations that affect the structure or expression of Toll-like receptor 2 may alter the host response to these pathogens. Identified functional polymorphisms in Toll-like receptor 2 between African Americans and Caucasians may thus directly create race-specific immunologic responses to Gram-positive infections that genetically predispose blacks to sepsis compared with whites (36). Therefore, the disparities that are observed are likely multifactorial, with partial explanations related to differences in chronic comorbid medical conditions, socioeconomic status, and genetics.

These data confirm that males are at >25% increased risk for developing sepsis compared with females. This disparity has also been reported for patients with severe sepsis, including patients from countries outside the United States (4, 6, 33, 37). The basis for these disparities has most frequently been postulated to relate to hormonal differences between genders, as traumatically injured males are more likely to develop sepsis and acute organ dysfunction compared with females with similar injuries (38). Estrogen levels in combination with plasma cytokine imbalance may contribute to the differences in the inflammatory response and the development of sepsis (39, 40), whereas hormonal manipulation in animal models has been shown to reduce the risk of death with sepsis for males compared with females (41). However, gender disparities also exist in the neonatal and pediatric sepsis populations (14–16), making hormonal differences an incomplete explanation. Furthermore, the observed increased risk specifically for Gram-positive infections among males compared with females after controlling for the site of infection suggests other contributing factors in the differential risk for sepsis. Investigators have begun to consider the genetic basis for gender differences in disease, with polymorphisms in the lipopolysaccharide-binding protein and tumor necrosis factor genes reported to alter the sepsis phenotype in males but not females (42, 43).

The development of acute organ dysfunction is a critical event in the evolution of sepsis, heralding the onset of severe sepsis and a poorer prognosis. Predictors of organ dysfunction include age, gender, immune status, and existence of underlying disease (7). The association of chronic comorbid medical conditions with acute organ dysfunction may simply reflect physiologic reserve, but it also merits clinical consideration because comorbidities are readily identifiable clinical variables associated with acute organ dysfunction and a worse prognosis. In addition, studies have shown that the type of infection (e.g., methicillin-resistant *Staphylococcus aureus*) and the site of infection influence the occurrence of acute organ dysfunction and subsequent clinical outcomes (18, 19). As such, Gram-positive infections appear to be less responsive to anti-inflammatory agents and result in more severe illness (44). The ability to predict the occurrence of acute organ dysfunction would be clinically relevant with potential therapeutic implications and could improve long-term outcomes or quality of life given the impact of organ dysfunction on mortality rate after discharge from the intensive care unit (45, 46).

The use of administrative datasets for critical care health services research is recognized as an essential tool, yet it has limitations that are partially offset by the large sample size of patient-level data (47, 48). The use of ICD-9CM codes to identify specific medical conditions has limitations but for sepsis has been validated to carry a positive predictive value of 88.9% and a sensitivity of 87.7% (2, 27, 49), yielding calculated specificity and negative predictive value to be 98.8% and 98.6%, respectively (2). Although ICD-9 coding schema may change over time, thus influencing incidence rates, longitudinal changes would be unlikely to vary by gender or race. We cannot determine mortality specifically attributable to sepsis, differentiate physician-specific practices relating to race or gender, or necessarily extrapolate these findings to patients outside the United States.

CONCLUSION

This study serves as a first step toward eliminating healthcare disparities in sepsis. In addition, the results may help to advance our understanding of the pathogenesis of sepsis, and they have implications for clinical trial analysis. The underlying reasons for disparities in sepsis are likely multifactorial, including the type and source of infection; distribution of chronic comorbid medical conditions; social, cultural and economic factors; and both access to health care and the delivery of health care. Although disparities have traditionally been considered in the context of social, economic, cultural, and healthcare differences, these data may generate new hypotheses regarding host susceptibility and genetic response to specific infectious stimuli that lead to sepsis. To more fully elucidate causes of disparities in sepsis, an optimal combination of prospective cohort studies and analyses from large administrative data is necessary. In the interim, clinicians can use this information in the treatment of patients with sepsis by better understanding the types and sources of infections in common patient groups and in better managing chronic comorbid conditions in high-risk patients.

Acknowledgments

Supported, in part, by grants HL K23-67739 (GSM) and AA R01-11660 (MM) from the National Institutes of Health, Bethesda, MD.

References

1. 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. [PubMed: 1303622]
2. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003; 348:1546–1554. [PubMed: 12700374]
3. 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. [PubMed: 7799491]
4. 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; 274:968–974. [PubMed: 7674528]
5. 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. [PubMed: 9218672]
6. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001; 29:1303–1310. [PubMed: 11445675]
7. Padkin A, Goldfrad C, Brady AR, et al. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med*. 2003; 31:2332–2338. [PubMed: 14501964]
8. Sundararajan V, Macisaac CM, Presneill JJ, et al. Epidemiology of sepsis in Victoria, Australia. *Crit Care Med*. 2005; 33:71–80. [PubMed: 15644651]
9. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001; 344:699–709. [PubMed: 11236773]
10. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis: A randomized controlled trial. *JAMA*. 2001; 286:1869–1878. [PubMed: 11597289]
11. Annane D, Seville V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002; 288:862–871. [PubMed: 12186604]

12. Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: A randomized controlled trial. *JAMA*. 2003; 290:238–247. [PubMed: 12851279]
13. Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med*. 2005; 353:1332–1341. [PubMed: 16192478]
14. Stoll BJ, Holman RC, Schuchat A. Decline in sepsis-associated neonatal and infant deaths in the United States, 1979 through 1994. *Pediatrics*. 1998; 102:e18. [PubMed: 9685463]
15. Bindl L, Buderus S, Dahlem P, et al. Gender-based differences in children with sepsis and ARDS: The ESPNIC ARDS Database Group. *Intensive Care Med*. 2003; 29:1770–1773. [PubMed: 12920510]
16. Watson RS, Carcillo JA, Linde-Zwirble WT, et al. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med*. 2003; 167:695–701. [PubMed: 12433670]
17. Bone RC. Toward an epidemiology and natural history of SIRS (systemic inflammatory response syndrome). *JAMA*. 1992; 268:3452–3455. [PubMed: 1460735]
18. Alberti C, Brun-Buisson C, Chevret S, et al. Systemic inflammatory response and progression to severe sepsis in critically ill infected patients. *Am J Respir Crit Care Med*. 2005; 171:461–468. [PubMed: 15531752]
19. Guidet B, Aegerter P, Gauzit R, et al. Incidence and impact of organ dysfunctions associated with sepsis. *Chest*. 2005; 127:942–951. [PubMed: 15764780]
20. 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; 28:108–121. [PubMed: 11907653]
21. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991; 100:1619–1636. [PubMed: 1959406]
22. Pittet D, Thievent B, Wenzel RP, et al. Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. *Intensive Care Med*. 1993; 19:265–272. [PubMed: 8408935]
23. Smedley, BD.; Stith, AY.; Nelson, AR. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academies Press; 2003.
24. National Healthcare Disparities Report. Agency for Healthcare Research and Quality; Feb. 2004 Available at: <http://www.ahrq.gov/qual/nhdr03/nhdrsum03.htm> [Accessed December 15, 2005]
25. [Accessed December 15, 2005] Healthy People. 2010. Available at: <http://www.healthypeople.gov/>
26. [Accessed December 15, 2005] National Hospital Discharge Survey description. Available at: <http://www.cdc.gov/nchs/about/major/hdasd/nhdsdes.htm>
27. Eaton S, Burnham E, Martin GS, et al. The ICD-9 code for septicemia maintains a high positive predictive value for clinical sepsis. *Am J Respir Crit Care Med*. 2002; 165:A471.
28. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–383. [PubMed: 3558716]
29. 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. [PubMed: 1607900]
30. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994; 47:1245–1251. [PubMed: 7722560]
31. [Accessed December 15, 2005] US Interim Projections by Age, Sex, Race and Hispanic Origin. Available at: <http://www.census.gov/ipc/www/usinterimproj>
32. User's Guide for SAS/STAT. 2. Cary, NC: SAS Institute; 1990.
33. Dombrovskiy V, Martin AA, Sunderram J, et al. Facing the challenge: decreasing case fatality rates in severe sepsis despite increasing hospitalizations. *Crit Care Med*. 2005; 33:2555–2562. [PubMed: 16276180]
34. Wong MD, Shapiro MF, Boscardin WJ, et al. Contribution of major diseases to disparities in mortality. *N Engl J Med*. 2002; 347:1585–1592. [PubMed: 12432046]
35. Schwartz RS. Racial profiling in medical research. *N Engl J Med*. 2001; 344:1392–1393. [PubMed: 11333999]

36. Yim JJ, Ding L, Schaffer AA, et al. A micro-satellite polymorphism in intron 2 of human Toll-like receptor 2 gene: functional implications and racial differences. *FEMS Immunol Med Microbiol*. 2004; 40:163–169. [PubMed: 14987735]
37. Lewis CA, Moss M, Martin GS. Temporal epidemiology of severe sepsis in the United States. *Proc Am Thorac Soc*. 2005; 2:A152.
38. Oberholzer A, Keel M, Zellweger R, et al. Incidence of septic complications and multiple organ failure in severely injured patients is sex specific. *J Trauma*. 2000; 48:932–937. [PubMed: 10823539]
39. Asai K, Hiki N, Mimura Y, et al. Gender differences in cytokine secretion by human peripheral blood mononuclear cells: Role of estrogen in modulating LPS-induced cytokine secretion in an ex vivo septic model. *Shock*. 2001; 16:340–343. [PubMed: 11699070]
40. Diodato MD, Knoferl MW, Schwacha MG, et al. Gender differences in the inflammatory response and survival following haemorrhage and subsequent sepsis. *Cytokine*. 2001; 14:162–169. [PubMed: 11396994]
41. Schneider CP, Nickel EA, Samy TS, et al. The aromatase inhibitor, 4-hydroxyandrostenedione, restores immune responses following trauma-hemorrhage in males and decreases mortality from subsequent sepsis. *Shock*. 2000; 14:347–353. [PubMed: 11028555]
42. Schroder J, Kahlke V, Book M, et al. Gender differences in sepsis: Genetically determined? *Shock*. 2000; 14:307–310. [PubMed: 11028548]
43. 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; 29:557–561. [PubMed: 11373419]
44. Opal SM, Cohen J. Clinical Gram-positive sepsis: Does it fundamentally differ from Gram-negative bacterial sepsis? *Crit Care Med*. 1999; 27:1608–1616. [PubMed: 10470773]
45. Azoulay E, Adrie C, De Lassence A, et al. Determinants of postintensive care unit mortality: A prospective multicenter study. *Crit Care Med*. 2003; 31:428–432. [PubMed: 12576947]
46. Johnston JA, Yi MS, Britto MT, et al. Importance of organ dysfunction in determining hospital outcomes in children. *J Pediatr*. 2004; 144:595–601. [PubMed: 15126992]
47. Pronovost P, Angus DC. Using large-scale databases to measure outcomes in critical care. *Crit Care Clin*. 1999; 15:615–viii. [PubMed: 10442267]
48. Moss M, Martin GS. A global perspective on the epidemiology of sepsis. *Intensive Care Med*. 2004; 30:527–529. [PubMed: 14985955]
49. Ollendorf DA, Fendrick AM, Massey K, et al. Is sepsis accurately coded on hospital bills? *Value Health*. 2002; 5:79–81. [PubMed: 11918823]

APPENDIX

Other comorbid conditions were identified by standard ICD-9CM codes: cancer (140.x–239.x), diabetes mellitus (250.x), chronic obstructive pulmonary disease (490.x–496.x), acquired immune deficiency syndrome/human immunodeficiency virus (042.x), hypertension (401.x), congestive heart failure (391.8, 398.9, 402.9, 425.0–425.7, 428.0–428.9, 429.3, 440.9, 648.6), coronary disease (36.0–36.1, 410.0–414.0, 429.2), chronic renal failure (585.0–585.9, 586.0–586.9), chronic hepatic failure (570.x–571.x, 572.2), and chronic alcohol abuse (303.x, 305).

The following codes were used to identify the source of infection causing sepsis: respiratory (010.0–011.9, 018, 034.0, 098.6, 461.0–513.9); genitourinary (098.17, 112.2, 590.0–616.9); skin, soft tissue, or bone (003.24, 015, 035, 036.82, 040.0, 095.5, 098.5, 680.0–686.9, 711.0–730.9); gastrointestinal (001.0–009.9, 129, 530.0–577.9); central nervous system (012.0, 036.0, 091.81, 094, 098.82, 320.0–326.9); cardiovascular (036.41–036.43, 093.0–093.82, 098.83–098.84, 391.2, 421.0–422.9); and other (958, 995.0–998.9).

Figure 1.

A, population-adjusted sepsis incidence rates by gender according to the source of infection. B, proportional distribution of sepsis between males and females according to the source of infection. *Resp*, respiratory; *GU*, genitourinary; *GI*, gastrointestinal.

Figure 2. Proportion of Gram-positive infections in males and females stratified by the source of infection. *Resp*, respiratory; *GU*, genitourinary; *GI*, gastrointestinal.

Figure 3.

A, population-adjusted sepsis incidence rates by race according to the source of infection. *B*, proportional distribution of sepsis cases between races according to the source of infection. *Resp*, respiratory; *GU*, genitourinary; *GI*, gastrointestinal.

Figure 4. Proportion of Gram-positive infections among races stratified by the source of infection. *Resp*, respiratory; *GU*, genitourinary; *GI*, gastrointestinal.

Figure 5.

A, distribution of chronic comorbid medical conditions in sepsis patients according to race. *B*, distribution of chronic comorbid medical conditions in sepsis patients according to gender. *COPD*, chronic obstructive pulmonary disease; *ESRD*, end-stage renal disease; *EtOH*, chronic alcohol abuse; *HIV*, human immunodeficiency virus.

Table 1

Characteristics of the sepsis population, stratified by gender and race

Characteristic	Total	Males	Females	White	Black	Other
Age	60.5 (60.4–60.7)	57.6 (57.4–57.9)	63.2 (62.9–63.4)	63.0 (62.8–63.2)	52.4 (52.0–52.8)	52.1 (51.3–52.9)
Length of stay	9.0 (8.9–9.1)	9.0 (8.8–9.1)	8.0 (7.8–8.1)	9.0 (8.9–9.1)	10.0 (9.7–10.3)	8.0 (7.5–8.6)
Organ dysfunction	0.40 (0.40–0.41)	0.42 (0.42–0.43)	0.38 (0.38–0.39)	0.37 (0.37–0.38)	0.46 (0.45–0.47)	0.49 (0.47–0.51)
Comorbidities	1.07 (1.07–1.08)	1.10 (1.09–1.11)	1.06 (1.05–1.07)	1.09 (1.08–1.10)	1.07 (1.06–1.09)	1.02 (1.00–1.05)
Charlson-Deyo score	1.45 (1.44–1.46)	1.54 (1.52–1.56)	1.37 (1.35–1.39)	1.45 (1.44–1.47)	1.52 (1.49–1.55)	1.40 (1.34–1.45)
Discharge status						
Home	49.8 (49.4–50.3)	51.5 (50.7–52.4)	48.2 (47.6–48.9)	48.4 (47.8–49.1)	52.1 (51.1–53.2)	60.6 (58.4–62.9)
Healthcare facility	22.4 (22.0–22.8)	20.6 (19.9–21.2)	24.0 (23.5–24.6)	23.6 (23.0–24.1)	19.0 (18.2–19.8)	15.3 (13.7–17.0)
Death	20.3 (19.9–20.6)	20.1 (19.4–20.8)	20.5 (20.0–21.0)	21.0 (20.5–21.6)	20.5 (19.7–21.4)	17.7 (15.9–19.5)
Other	7.5 (7.3–7.8)	7.8 (7.4–8.3)	7.3 (7.0–7.6)	7.0 (6.7–7.3)	8.3 (7.8–8.9)	6.3 (5.2–7.5)

Values presented are means, medians, or proportions with 95% confidence intervals in parentheses, as described next: age, mean patient age (yrs); length of stay, median duration of hospital length of stay (days); organ dysfunction, mean number of dysfunctional organ systems; comorbidities, mean number of chronic comorbid medical conditions; Charlson-Deyo score, mean value of Charlson-Deyo comorbidity index; discharge status, proportion (%) of sepsis patients who were discharged to home or to another healthcare facility, who died, or for whom discharge status was otherwise stated (either hospitalization terminated against medical advice or discharge status unknown).