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Temporal Trends in the Epidemiology of Severe Postoperative Sepsis after Elective Surgery

A Large, Nationwide Sample

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CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Introduction: Multiple studies have used administrative datasets to examine the epidemiology of sepsis in general, but the entity of postoperative sepsis has been studied less intensively. Therefore, we undertook an analysis of the epidemiology of postoperative sepsis using the Nationwide Inpatient Sample, the largest in-patient dataset available in the United States.

Methods: Elective admissions of patients aged 18 yr or older with a length of stay more than 3 days for any 1 of the 20 most common elective operative procedures were extracted from the dataset for the years 1997–2006. Postoperative sepsis was defined using the appropriate International Classification of Diseases, Ninth Revision, Clinical Modification codes; severe sepsis was defined as sepsis along with organ dysfunction. Logistic regression was used to assess the significance of temporal trends after adjusting for relevant demographic characteristics, operative procedure, and comorbid conditions.

Results: We identified 2,039,776 admissions for analysis. The rate of severe sepsis increased from 0.3% in 1997 to 0.9% in 2006. This trend persisted after adjusting for relevant covariables—the adjusted odds ratio of severe sepsis per year increase in the study period was 1.12 (95% CI, 1.11–1.13; $P < 0.001$). The in-hospital mortality rate for patients with severe postoperative sepsis declined from 44.4% in 1997 to 34.0% in 2006; this trend also persisted after adjustment for relevant covariables—the adjusted odds ratio per year was 0.94 (95% CI, 0.93–0.95; $P < 0.001$).

Conclusion: During the 10-yr period that we studied, there was a marked increase in the rate of severe postoperative sepsis but a concomitant decrease in the in-hospital mortality rate in severe sepsis.

What We Already Know about This Topic

- Large administrative datasets have been queried to examine trends in sepsis in general, but little is known about trends in sepsis following elective surgery

What This Article Tells Us That Is New

- In over 2 million patients in the US Nationwide Inpatient Sample from 1997 to 2006, the incidence of severe postoperative sepsis increased from 0.3% to 0.9%
- Over that same time, mortality from severe postoperative sepsis decreased by over 10%

SEPSIS is an important source of postoperative morbidity and mortality. Although administrative datasets have been used extensively to define the epidemiology of sepsis in general,[1–5] postoperative sepsis has been studied less inten-

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sively; the studies that exist are generally limited to single centers[6,7] or based on data from a single state.[8]

During the past decade, there has been a substantial increase in the incidence of severe sepsis in the general population,[1,3,4] along with an increase in the rates of antibiotic resistance in nosocomial infections.[9,10] There has also been an increased understanding of factors contributing to nosocomial infection and efforts to reduce them.[11–15] Furthermore, this decade has seen a number of important studies[16–21] and guidelines[22] that have modified the approach to treating patients who develop severe sepsis. These findings suggest the need to appraise trends in the incidence of and outcomes from severe postoperative sepsis.

The purpose of this study was to assess, using the largest administrative dataset of admissions available in the United States, the Nationwide Inpatient Sample (NIS), temporal trends in severe postoperative sepsis after elective surgery.

Materials and Methods

Study Data Source

Data for the study were obtained from the NIS, an administrative dataset created by the Agency for Healthcare Research and Quality as part of the Healthcare Utilization Project.[23] It contains approximately 8 million discharges annually for the time period considered in our study, representing approximately 20% of all hospitalizations in non-Federal, acute care hospitals in the United States. To generate a sample that is optimized to be representative of all U.S. hospitalizations, hospitals were selected to contribute data to the NIS based on five characteristics. These include bed size, ownership, location (urban or rural), teaching status, and geographic region. The database includes information on each discharge, including patients' age, race, gender, up to 15 diagnoses and procedures (coded using International Classification of Disease—Clinical Modification, Ninth Revision [ICD-9-CM]), cost of the hospitalization, length of stay, and the discharge destination. Also included for approximately 90% of hospitalizations is whether the admission is emergent, urgent, or elective in nature.

Definition of the Most Common Elective Surgical Procedures

To identify the most commonly performed elective surgical procedures, we ascertained the relative frequency of the primary procedure type (as defined by the Clinical Classification Software categories, which combine procedures based on ICD-9 codes in a limited number of clinically relevant groups[24]) among elective admissions with a length of stay more than 3 days using the 2006 NIS dataset. We limited our analysis to admissions with a length of stay more than 3 days because (1) this selects for admissions for the major surgical procedures that are likely to confer a significant risk of sepsis, (2) it excludes patients who are quickly discharged from the index hospitalization before signs and symptoms of postoperative infection are likely to manifest, and (3) the Agency for Healthcare Research and Quality patient safety indicator measure of postoperative sepsis is applied only to hospitalizations with a length of stay more than 3 days.[25] We excluded admissions for medical, obstetrical, wound care, and other nonoperative indications, and the remaining top 20 most frequently performed primary procedure types were defined as the surgical procedures of interest (see Supplemental Digital Content 1, http://links.lww.com/ALN/A579).

Study Population

We selected for analysis all elective admissions of patients aged 18 yr or older for any of the 20 most common primary procedure types who had a length of stay more than 3 days from the NIS dataset for the years 1997–2006. Because the primary diagnosis in the discharge abstract represents the reason for hospitalization and because the focus of our study is on sepsis that developed postoperatively, we excluded all admissions with a primary diagnosis indicating an infectious process.

Study Variables

Postoperative sepsis was defined by any of the following ICD-9-CM codes recorded as a secondary diagnosis—streptococcal septicemia (038.0), staphylococcal septicemia (038.1), pneumococcal septicemia (038.2), anaerobe septicemia (038.3), Gram-negative septicemia (038.4), other specified septicemia (038.8), unspecified septicemia (038.9), systemic candidiasis (112.5), systemic inflammatory response syndrome due to infectious process without organ dysfunction (995.91), systemic inflammatory response syndrome due to infectious process with organ dysfunction (995.92), and septic shock (785.52).

For our study, severe sepsis was defined, in accordance with 1991 and 2001 sepsis consensus conference guidelines, as sepsis complicated by organ dysfunction.[26,27] The presence of organ dysfunction was defined, in the following six organ systems, by the presence of the appropriate ICD-9-CM codes with appropriate subcodes—respiratory (518.5, 518.81, 518.82, 518.84, 786.09, and 799.1), cardiovascular (427.5, 458.0, 458.8, 458.9, 796.3, and 785.5), coagulation (287.4, 287. 5, 286.6, and 286.9), renal (584), hepatic (570, 572.2, and 573.4), and central nervous system (293.0, 348.1, 348.3, and 780.01).[4]

Patient demographic variables, which may influence the risk for sepsis, including age, gender, and race, were recorded directly from the dataset. Data on race were not reported for 29.3% of patients and were recorded as "missing." The characteristics of the hospitals in which patients in our cohort were treated were also determined, including whether the hospital was a teaching institution (generally defined as hospitals with a ratio of full-time residents to hospital beds of ≥0.25) and the hospital bed size (classified as small, medium, or large, with cutoffs for each group that are specific to the region, teaching status, and rural or urban location of the institutions).[23] Similarly, various comorbid conditions, which may be risk factors for sepsis, were ascertained using the appropriate ICD-9-CM codes, including chronic pulmonary disease, congestive heart failure, chronic renal disease, chronic liver disease, and metastatic malignancy. Each of the 20 procedure types that our cohort underwent was reclassified into nine surgery classes for purposes of analysis, as shown in Supplemental Digital Content 1, http://links.lww.com/ALN/A579.

The NIS does not contain information regarding the severity of critical illness, such as Acute Physiology and Chronic Health Evaluation scores or similar scores. Therefore, to obtain some gauge of the severity of illness in patients classified as having severe sepsis and to determine how this varied by year, we ascertained the rates of hemodialysis and prolonged mechanical ventilation ($>$ 96 consecutive hours), using appropriate ICD-9-CM procedure codes.

To help define the extent to which the increase in recorded postoperative sepsis may reflect a broader trend toward more aggressive coding of postoperative complications, we queried for the occurrence of acute postoperative myocardial infarction, postoperative stroke, and postoperative gastric ulceration among the secondary diagnoses in our surgical cohort and determined the rates of these complications for each year in the study period.

To ascertain the excess hospital charges associated with severe sepsis, we first calculated, by year, the mean total hospital charge for each of the 20 procedure types (using the Clinical Classifications Software classifications) considered in our study. Excess charge was then determined for each patient with severe sepsis by subtracting the mean charge for the patient's procedure type for that year from the patient's total charges. The mean excess charges were then calculated among patients with severe sepsis for each year of the study period. All hospital charges are adjusted for inflation and reported in 2006 U.S. dollars. Hospital charges, as reported in the NIS, do not include professional fees.

Statistical Analysis

An unadjusted test for trend was performed for continuous outcomes using linear regression (including excess total hospital charges) and for binary outcomes (including sepsis, severe sepsis, or in-hospital death) using univariate logistic regression. Multivariable logistic regression models were used to assess for temporal trends in the incidence of severe sepsis and for in-hospital mortality in patients who develop severe sepsis after adjusting for various potential confounding variables. Variables were selected for inclusion in the model based on the clinical plausibility that they would have an effect on the occurrence of and outcome from severe sepsis and therefore may be explanatory of the trends that we observed. These variables included surgical procedure class, patient age, race, gender, comorbidities, and hospital characteristics, including bed size and teaching status. The comorbidities were selected for inclusion in the model based on their well-recognized role as risk factors for severe sepsis. Because all variables are of clinical relevance to the occurrence and outcomes from sepsis, they were forced into the model. Results from the multivariate analysis were reported as odds ratios and corresponding 95% CI. Statistics were performed using SPSS (SPSS, Inc., Version 11.5, Chicago, IL) and STATA (StataCorp LP, Version 10.0, College Station, TX). Statistical significance was judged as P less than 0.05.

Results

For the 10-yr period from 1997 to 2006, we identified 2,039,776 elective admissions of patients aged 18 yr or older, with a length of stay more than 3 days, who underwent 1 of the 20 most common elective surgical procedures. There were between 713 and 776 hospitals annually who contributed discharge data used in this study. The types of procedures included in the study are shown in Supplemental Digital Content 1, http://links.lww.com/ALN/A579. Table 1 shows the baseline characteristics of the entire surgical population stratified by 2-yr intervals of the study period. We tested for trend for each of the comorbidities listed; the rates of all the comorbities increased over time ($P < 0.001$), except metastatic malignancy, which declined ($P < 0.001$).

Overall, there were 17,864 cases of postoperative sepsis for a rate of 0.9% and 10,731 cases of severe postoperative sepsis for a rate of 0.5%. Of the patients with severe sepsis, renal failure was coded in 43.0%, respiratory dysfunction in 69.8%, cardiovascular dysfunction in 31.6%, coagulation dysfunction in 17.0%, hepatic dysfunction in 4.0%, and neurologic dysfunction in 4.8%. Organ dysfunction in a single system was noted in 51.3%, two systems in 31.4%, and three or more systems in 17.3% of patients with severe sepsis. Pneumonia was coded as a concomitant diagnosis in 35.2%, implant or line infection in 11.8%, urinary tract infection in 12.0%, and other postoperative infection (including infected seroma, intraabdominal or subphrenic abscess, and wound infection) in 18.0% of patients with severe sepsis.

Figure 1 shows the rate of postoperative sepsis and severe sepsis for each year in the study period; the rate of postoperative sepsis increased from 0.7% in 1997 to 1.3% in 2006 ($P < 0.001$), and the rate of severe postoperative sepsis increased from 0.3% in 1997 to 0.9% in 2006 ($P < 0.001$). The increasing rate of severe sepsis was consistent across the various classes of surgical procedures considered in our study, as demonstrated in figure 2. When all elective admissions for the surgical procedures of interest were considered (and not just those patients with a length of stay of $>$ 3 days), the rate of severe sepsis increased from 0.2% in 1997 to 0.4% in 2006 ($P < 0.001$).

Table 2 shows the results of the multivariate logistic regression model examining predictors of severe postoperative sepsis. The model showed that the temporal trend persisted (odds ratio, 1.12; 95% CI, 1.11–1.13 per year increase in the study period; $P < 0.001$) even after adjusting for potential confounding variables. The model also showed increasing age, African American race, and Hispanic ethnicity (*vs.* white), chronic pulmonary disease, congestive heart failure,

Table 1. Baseline Characteristics of the Surgical Cohort, Stratified by 2-yr Intervals of the Study Period

	1997–1998 N (%)	1999–2000 N (%)	2001–2002 N (%)	2003–2004 N (%)	2005–2006 N (%)
Surgery class					
Cardiac	64,041 (16.9)	72,299 (18.2)	76,656 (17.6)	70,301 (16.5)	63,429 (15.8)
Gynecologic	33,625 (8.9)	28,048 (7.1)	27,135 (6.2)	24,105 (5.6)	20,865 (5.2)
Joint replacement	99,001 (26.2)	103,815 (26.2)	120,855 (27.8)	119,559 (28.0)	122,378 (30.4)
Lower gastrointestinal	55,423 (14.7)	59,312 (15.0)	65,211 (15.0)	64,235 (15.0)	60,402 (15.0)
Spine	34,288 (9.1)	37,154 (9.4)	43,286 (9.9)	46,087 (10.8)	45,888 (11.4)
Thoracic	14,101 (3.7)	14,134 (3.6)	15,141 (3.5)	15,097 (3.5)	15,730 (3.9)
Upper gastrointestinal	25,569 (6.8)	27,491 (6.9)	32,427 (7.4)	34,551 (8.1)	26,971 (6.7)
Urologic	14,605 (3.9)	15,357 (3.9)	16,304 (3.7)	16,688 (3.9)	15,851 (3.9)
Vascular	37,494 (9.9)	38,740 (9.8)	38,368 (8.8)	36,640 (8.6)	31,119 (7.7)
Age, yr					
$<$ 55	95,852 (25.3)	102,803 (25.9)	115,390 (26.5)	112,364 (26.3)	98,789 (24.5)
55–64	70,807 (18.7)	78,802 (19.9)	89,120 (20.5)	93,405 (21.9)	92,139 (22.9)
65–74	115,882 (30.6)	114,690 (28.9)	121,595 (27.9)	116,206 (27.2)	110,577 (27.5)
75–84	81,588 (21.6)	84,817 (21.4)	92,872 (21.3)	89,387 (20.9)	85,418 (21.2)
$>$ 84	14,018 (3.7)	15,238 (3.8)	16,406 (3.8)	15,901 (3.7)	15,710 (3.9)
Female gender*	209,026 (55.3)	215,970 (54.5)	240,977 (55.3)	238,475 (55.8)	224,997 (55.9)
Race					
White	247,110 (65.3)	248,614 (62.7)	238,362 (54.7)	243,517 (57.0)	227,786 (56.6)
African-American	24,087 (6.4)	23,561 (5.9)	26,053 (6.0)	27,939 (6.5)	23,381 (5.8)
Hispanic	9,223 (2.4)	9,983 (2.5)	15,545 (3.6)	16,028 (3.8)	14,997 (3.7)
Asian and Pacific Islander	1,303 (0.3)	1,699 (0.4)	2,091 (0.5)	2,464 (0.6)	2,482 (0.6)
Native Americans	466 (0.1)	499 (0.1)	1,076 (0.2)	529 (0.1)	1,126 (0.3)
Other	4,609 (1.2)	6,172 (1.6)	6,780 (1.6)	7,696 (1.8)	6,216 (1.5)
Missing	91,349 (24.2)	105,822 (26.7)	145,476 (33.4)	129,090 (30.2)	126,645 (31.5)
Chronic pulmonary disease†	54,089 (14.3)	59,165 (14.9)	70,342 (16.2)	75,314 (17.6)	77,844 (19.3)
Congestive heart failure†	27,494 (7.3)	28,908 (7.3)	32,721 (7.5)	34,886 (8.2)	33,506 (8.3)
Chronic renal disease†	11,505 (3.0)	12,931 (3.3)	14,568 (3.3)	15,659 (3.7)	20,960 (5.2)
Chronic liver disease†	2,537 (0.7)	2,620 (0.7)	3,427 (0.8)	3,965 (0.9)	3,528 (0.9)
Metastatic malignancy†	18,595 (4.9)	16,628 (4.2)	17,121 (3.9)	16,659 (3.9)	15,545 (3.9)
Bed size of hospital*					
Small	39,616 (10.5)	37,060 (9.4)	48,187 (11.1)	46,974 (11.0)	45,512 (11.3)
Medium	96,991 (25.7)	100,710 (25.4)	93,693 (21.5)	96,099 (22.5)	91,714 (22.8)
Large	240,773 (63.8)	258,382 (65.2)	293,503 (67.4)	284,114 (66.5)	265,168 (65.9)
Teaching hospital	205,582 (54.5)	215,093 (54.3)	233,973 (53.7)	225,369 (52.8)	205,131 (51.0)

* Gender was not reported in 137 admissions and hospital characteristics in 1,280 admissions. † Test for trend ($P < 0.001$).

chronic renal disease, chronic liver disease, metastatic malignancy, and treatment at a hospital with large bed size (*vs.* small bed size) to be significant independent predictors of severe postoperative sepsis, whereas female gender was found to be protective for the development of severe sepsis. When the logistic regression analysis was performed excluding cases of hysterectomy, female gender continued to be protective for the development of severe sepsis ($P < 0.001$).

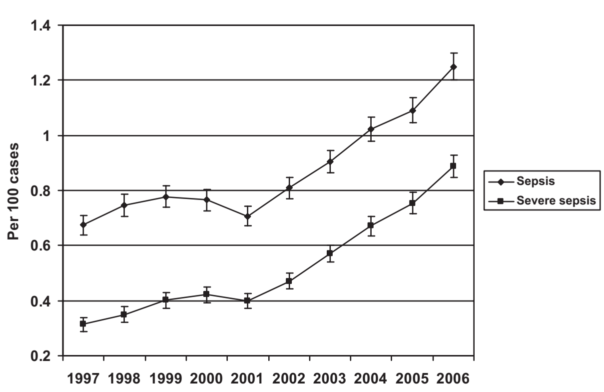

Fig. 1. The rate of postoperative sepsis and severe postoperative sepsis (defined as sepsis with organ dysfunction) and 95% confidence interval, by year, for our surgical cohort.

Of the 10,701 patients with severe postoperative sepsis for whom mortality data were coded, 4,210 (39.3%) died. Figure 3 shows the in-hospital mortality rate for patients with severe sepsis by year; it declined during the study period from 44.4% in 1997 to 34.0% in 2006 ($P < 0.001$). This trend persisted after adjusting for potential confounders in a multivariate logistic regression model (odds ratio, 0.94; 95% CI, 0.93–0.95 per year increase in the study period; $P < 0.001$). As shown in table 3, the model also showed increasing age, chronic renal disease, chronic liver disease, metastatic malignancy, and treatment at large or medium bed size hospitals (*vs.* small bed size hospitals) or teaching hospitals to be predictive of in-hospital mortality for patients with severe sepsis.

The mean excess charge associated with severe sepsis increased from 119,337 ± 144,705 in 1997 to 157,882 ±

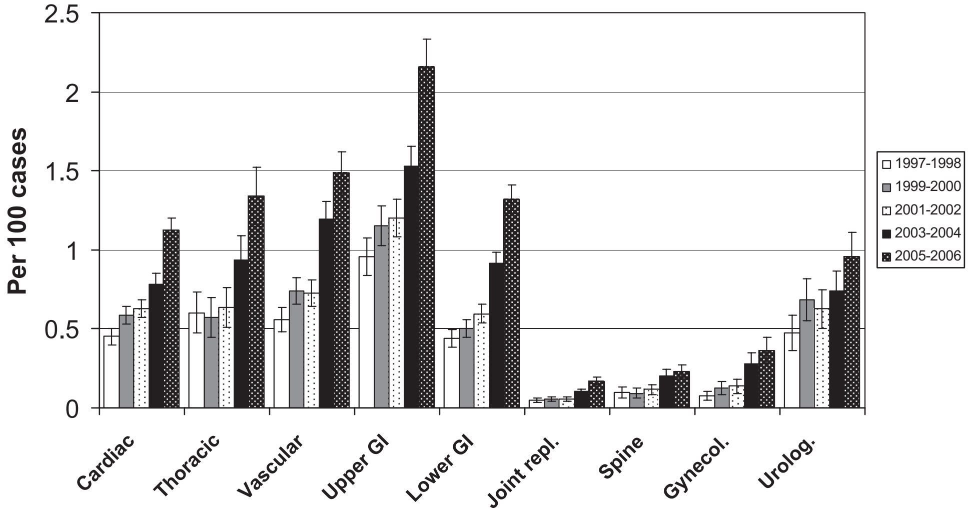

Fig. 2. The rate of severe postoperative sepsis for each surgery class, stratified by 2-yr intervals of the study period. GI = gastrointestinal surgery; Gynecol = gynecologic; Joint repl = joint replacement; Urolog = urologic.

162,999 in 2006 (in 2006 U.S. dollars). Linear regression analysis showed this trend to be highly significant (β coefficient, 6,565; 95% CI, 5,581–7,550; $P < 0.001$).

Figure 4 shows the rates and 95% CI, by year, of hemodialysis and prolonged mechanical ventilation (defined as > 96 consecutive hours) in patients with severe postoperative sepsis. Rates of both were relatively constant across the study period.

Supplemental Digital Content 2 shows the rates of postoperative myocardial infarction, postoperative stroke, and gastric ulceration, http://links.lww.com/ALN/A580. There was a small, but statistically significant, decline in each of these postoperative complications during the study period ($P < 0.001$ for each complication).

Discussion

This study uses the largest administrative dataset of hospital admissions in the United States to examine temporal trends in the incidence and outcomes of severe sepsis after elective surgery for the years 1997–2006. We report not only a near threefold increase in the incidence of severe sepsis among postoperative patients with a length of stay of more than 3 days but also observe an approximately 10% absolute decline in in-hospital mortality among patients who develop severe sepsis. These trends persisted and were highly significant even after adjusting for potentially confounding variables, including surgery type, patient demographics and comorbidities, and hospital characteristics.

Our findings concur with the results of other studies that examined trends in the incidence of sepsis in the general population using statewide and nationwide datasets.[1,3,4] These studies have reported, during time periods that overlap with those considered in our study, a substantial increase in the rate of severe sepsis and a decline in the case-fatality rate associated with severe sepsis. For example, Dombrovskiy *et al.* used the NIS to show that from 1993 to 2003, the age-adjusted rate of hospitalization for severe sepsis increased from 66.8 to 132.0 cases per 100,000 persons, whereas the in-hospital case-fatality rate decreased from 45.8% to 37.8%.[4] A study that examined postoperative sepsis in all surgical admissions using statewide data from New Jersey (in contrast to our study, which considered a well-defined group of elective surgical procedures in a nationwide sample) found that from 1990 to 2006, the incidence of severe sepsis increased from 1.79% to 3.15% after nonelective surgery and from 0.22% to 1.12% after elective surgery.[8]

There are several possible reasons for the increased rate of postoperative sepsis. Studies have documented an increase in the proportion of nosocomial infections caused by resistant organisms during the time frame of our study,[9,10] and this may be implicated in the increased incidence of severe sepsis. Furthermore, the rates of many of the comorbidities that predispose to sepsis that were considered in our study increased, suggesting that patients undergoing the elective procedures are increasingly more ill at baseline. We did consider the possibility that trends toward shorter length of hospitalization might enrich the proportion of patients who had severe sepsis in the group whose length of stay was more than 3 days. However, the increase in the rate of severe sepsis was similar, and the trend was highly significant when all patients undergoing the surgical procedures of interest (and not just those with a length of stay of > 3 days) were considered.

The substantial reduction in the case-fatality rate that we observed is encouraging, although this is tempered by the fact that, owing to the increasing incidence, the number of patients dying from severe sepsis after elective surgery is growing. Again, because of the lack of clinical detail in the NIS, we cannot conclusively determine the reason for the decline in the case-fatality rate. However, the study period saw the publication of a number of important studies that have changed the approach to patients with critical illness and severe sepsis[16–19,21] and widely promoted guidelines for

Table 2. Rates of Severe Postoperative Sepsis Are Shown by Surgical Class, Patient Demographic and Comorbidity Variables, and Hospital Characteristics, and the Results of the Multivariable Logistic Regression Showing the Adjusted Odds of Developing Severe Postoperative Sepsis

	N (%)	Odds Ratio	95% CI	*P* Value
Per year increase in the study period		1.12	1.11–1.13	< 0.001
Surgery type				
Joint replacement	505 (0.1)	Ref		
Spine	317 (0.2)	1.96	1.70–2.25	< 0.001
Thoracic	614 (0.8)	8.47	7.51–9.56	< 0.001
Cardiac	2,455 (0.7)	5.51	5.00–6.08	< 0.001
Vascular	1,675 (0.9)	6.46	5.84–7.16	< 0.001
Lower gastrointestinal	2,312 (0.8)	8.14	7.38–8.97	< 0.001
Upper gastrointestinal	2,061 (1.4)	15.9	14.3–17.5	< 0.001
Urologic	551 (0.7)	6.80	6.02–7.69	< 0.001
Gynecologic	241 (0.2)	3.00	2.57–3.52	< 0.001
Age, yr				
< 55	1,838 (0.4)	Ref		
55–64	2,038 (0.5)	1.33	1.24–1.41	< 0.001
65–74	3,295 (0.6)	1.61	1.52–1.71	< 0.001
75–84	2,945 (0.7)	1.83	1.72–1.94	< 0.001
> 84	615 (0.8)	1.85	1.68–2.04	< 0.001
Female gender	4,774 (0.4)	0.78	0.75–0.81	< 0.001
Race				
White	6,246 (0.5)	Ref		
African-American	828 (0.7)	1.25	1.16–1.35	< 0.001
Hispanic	442 (0.7)	1.13	1.02–1.25	0.015
Asian or Pacific Islander	71 (0.7)	1.20	0.94–1.51	0.141
Native American	31 (0.8)	1.39	0.97–1.99	0.072
Other	188 (0.6)	1.14	0.98–1.32	0.086
Missing	2,925 (0.5)	0.93	0.89–0.97	0.001
Chronic pulmonary disease	2,623 (0.8)	1.15	1.09–1.20	< 0.001
Congestive heart failure	3,057 (1.9)	3.24	3.09–3.39	< 0.001
Chronic renal disease	1,568 (2.1)	2.46	2.32–2.61	< 0.001
Chronic liver disease	269 (1.7)	1.82	1.61–2.06	< 0.001
Metastatic malignancy	788 (0.9)	1.28	1.18–1.38	< 0.001
Bed size of hospital				
Small	931 (0.4)	Ref		
Medium	2,330 (0.5)	1.04	0.97–1.13	0.281
Large	7,467 (0.6)	1.13	1.05–1.21	0.001
Teaching hospital	5,771 (0.5)	1.01	0.97–1.05	0.573

Data on one or more variables were missing (excluding race) for 1,417 (0.1%), and these were excluded from analysis.
CI = confidence interval.

the treatment of the septic patient,[22,28] which together may account for the observed reduction.

Our logistic regression analysis demonstrated several patient demographic characteristics that influenced the risk of severe sepsis. Female gender substantially decreased the risk for developing severe sepsis, independent of other patient and surgical risk factors. This diminished risk has been consistently reported in other epidemiologic studies of sepsis.[1–4] Laboratory data suggest that hormonal and genetic factors may be involved,[29,30] but the biologic basis for this disparity remains relatively unclear. Given the significant effect size of gender in modulating risk, more work is clearly needed in this area. Similarly, our study found that African American race conferred an increased risk of sepsis, which reflects the findings of population-based studies.[1,3,4,31] Whether this is explained by differences in predisposing comorbidities, disparities in care, or genetic factors is a topic that deserves further investigation.

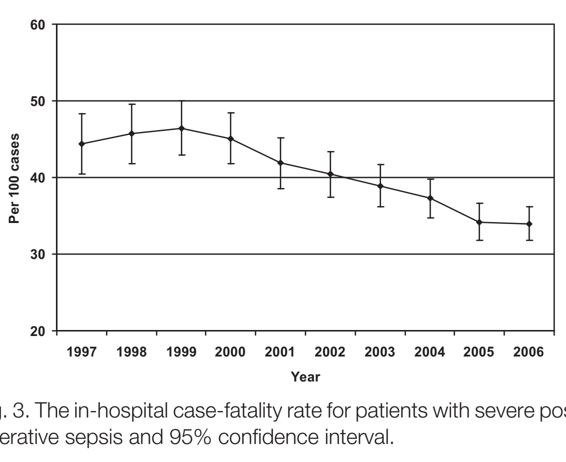

Fig. 3. The in-hospital case-fatality rate for patients with severe postoperative sepsis and 95% confidence interval.

Our study has a number of important limitations. First, it is retrospective and dependent on the recording of sepsis and organ dysfunction diagnoses in the discharge abstract by medical coders. As for most discharge coding, there are no strict criteria for applying the ICD-9-CM diagnoses for sep-

Table 3. Rates of In-hospital Mortality among Patients with Severe Postoperative Sepsis Are Shown by Surgical Class, Patient Demographic and Comorbidity Variables, and Hospital Characteristics, and the Results of the Multivariable Logistic Regression Showing the Adjusted Odds of Death for Patient with Severe Postoperative Sepsis

	N (%)	Odds Ratio	95% CI	*P* Value
Per year increase in the study period		0.94	0.93–0.95	< 0.001
Surgery type				
Joint replacement	139 (27.5)	Reference		
Spine	81 (25.6)	1.03	0.74–1.43	0.874
Thoracic	345 (56.6)	3.77	2.90–4.90	< 0.001
Cardiac	1,088 (44.5)	2.15	1.73–2.68	< 0.001
Vascular	695 (41.7)	1.89	1.51–2.37	< 0.001
Lower gastrointestinal	841 (36.4)	1.52	1.22–1.89	< 0.001
Upper gastrointestinal	775 (37.7)	1.73	1.39–2.16	< 0.001
Urologic	170 (31.0)	1.11	0.84–1.46	0.456
Gynecologic	76 (31.5)	1.31	0.92–1.86	0.134
Age, yr				
< 55	448 (24.4)	Reference		
55–64	709 (34.9)	1.66	1.44–1.92	< 0.001
65–74	1,336 (40.7)	2.15	1.88–2.46	< 0.001
75–84	1397 (47.5)	3.05	2.67–3.50	< 0.001
> 84	320 (52.3)	4.08	3.35–4.98	< 0.001
Female gender (*vs.* male)	1,854 (38.9)	1.04	0.96–1.13	0.327
Race				
White	2,468 (39.6)	Reference		
African-American	314 (38.2)	1.05	0.90–1.23	0.532
Hispanic	157 (35.8)	0.88	0.72–1.09	0.245
Asian or Pacific Islander	31 (43.7)	1.30	0.80–2.12	0.292
Native American	*	0.54	0.22–1.31	0.176
Other	76 (40.4)	1.06	0.78–1.44	0.714
Missing	1,157 (39.6)	1.05	0.95–1.15	0.332
Chronic pulmonary disease	1,037 (39.6)	0.91	0.82–1.00	0.049
Congestive heart failure	1,292 (42.4)	1.05	0.96–1.16	0.261
Chronic renal disease	677 (43.3)	1.26	1.12–1.42	< 0.001
Chronic liver disease	154 (57.2)	2.97	2.30–3.84	< 0.001
Metastatic malignancy	379 (48.3)	1.68	1.44–1.96	< 0.001
Bed size of hospital				
Small	321 (34.8)	Reference		
Medium	896 (38.6)	1.22	1.03–1.44	0.019
Large	2,992 (40.1)	1.32	1.13–1.53	< 0.001
Teaching hospital (*vs.* nonteaching hospital)	2,365 (41.1)	1.24	1.14–1.35	< 0.001

Data on one or more variables were missing (excluding race) for 34 (0.3%), and these were excluded from analysis.
* Cannot be shown, given Nationwide Inpatient Sample regulations regarding the disclosure of small cell sizes.
CI = confidence interval.

sis. Although Martin et al.[1] validated the main ICD-9 diagnosis code for sepsis (038.xx) and showed that it had a positive predictive value of 97.7% and a negative predictive value of 80.0%, we cannot exclude the possibility that hospitals differ in the accuracy with which they record the diagnosis of sepsis or that the accuracy has changed over time. The period of time covered in our study was coincident with the initiation of the Surviving Sepsis Campaign (in 2001) and with the introduction of drotrecogin-α into clinical practice (in 2002), which brought with it an aggressive pharmaceutical advertising campaign promoting the diagnosis and treatment of sepsis. Although it seems unlikely that this alone would result in the threefold increase in the rate of severe sepsis that we observed, it is impossible to assess the effect of these external forces on the diagnosis and coding of sepsis. We did attempt to ensure that the higher rate of postoperative sepsis was not part of a broader trend to code postoperative complications more intensively by examining trends in postoperative myocardial infarction, stroke, and gastric ulceration and found that the recorded rates of these complications, in fact, declined. Another potential confounding issue is the introduction of new ICD-9-CM codes for sepsis (995.91 and 995.92) in 2002 and for septic shock (785.52) in 2003. However, these codes are intended for use in combination with the ICD-9 codes for systemic infection (038.xx, 112.5) that were present throughout our study period,[32] and indeed, for the years 2002–2006, only 4.7% of cases of severe sepsis was documented using the new sepsis codes in the absence of a systemic infection code.

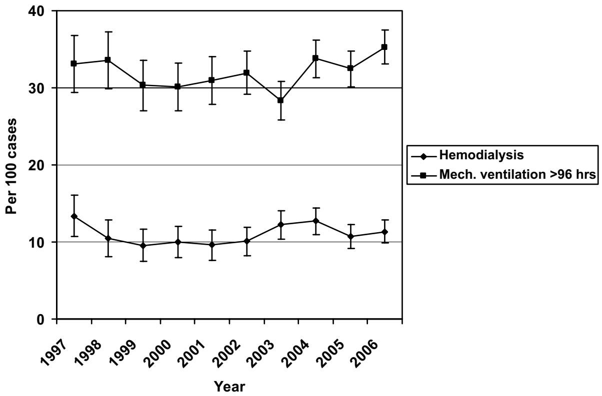

Fig. 4. The rate of hemodialysis and mechanical ventilation for more than 96 consecutive hours and 95% confidence interval for patients with severe postoperative sepsis.

Because the focus of our study was on changes in the rates of postoperative infection, we excluded from consideration all urgent and emergent surgical admissions—admission types that are likely to have a number of surgical indications that are infectious in nature. We also excluded all admission for which admission type was not coded and, in doing so, eliminated a fraction (~1/10) of NIS hospitalizations. Because, in its complete form, the NIS is a stratified sample that is designed to be maximally representative of all U.S. hospitalizations, by eliminating this fraction, we compromise, to some extent, the representativeness of the sample. This may introduce an element of confounding because the composition (*i.e.*, hospital bed size, teaching status, and region) of the subsample that we select may vary from year to year, in ways that are not reflective of changes in U.S. hospitalizations generally. To help compensate for this, we adjusted for hospital characteristics in our logistic regression model.

Although we attempted to control for the presence of patient comorbidities in our logistic regression analysis of trends, the ICD-9-CM codes that we used to identify comorbid illness are likely not completely sensitive for these diseases and do not generally grade the severity of the comorbid conditions. Furthermore, there are other patient variables (including body mass index and institutionalized living) and surgical factors (including length of surgery and extensiveness of procedure) that are likely to be relevant, and potentially confounding, which are not captured in the NIS and therefore are not adjusted for in our analyses.

Another limitation we face, particularly when examining trends in case-fatality rate, is that we do not have measures of the severity of illness of patients in the severe sepsis group, such as an Acute Physiology and Chronic Health Evaluation score. It is possible that the decline in in-hospital mortality reflects less ill patients being classified as having severe sepsis. Therefore, we examined the rates, by year, of hemodialysis and prolonged mechanical ventilation in patients with severe postoperative sepsis as a surrogate for illness severity. We found that rates of these procedures did not significantly vary across the study period, suggesting a relatively constant level of illness among patients in our study classified as having severe sepsis. Thus, the lower mortality in the severe sepsis cohort likely represents true gains in the effectiveness of treatment.

In conclusion, severe sepsis represents an increasingly important source of mortality after major elective surgery. During the 10-year period that we studied, the incidence of this complication has markedly increased, independent of changes in patient demographics, comorbidities, and surgery type. Further work is needed to confirm and understand the basis for this trend, but our data suggest the need for improved methods and practices of nosocomial infection control in the perioperative period.

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