Hospital Case Volume and Outcomes among Patients Hospitalized with Severe Sepsis

Allan J. Walkey¹ and Renda Soylemez Wiener^{1,2,3}

¹The Pulmonary Center, Boston University School of Medicine and Division of Pulmonary, Allergy, and Critical Care Medicine, Boston Medical Center, Boston, Massachusetts; ²Center for Healthcare Organization and Implementation Research, Edith Nourse Rogers Memorial VA Hospital, Bedford, Massachusetts; and ³The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth Medical School, Hanover, New Hampshire

Abstract

Rationale: Processes of care are potential determinants of outcomes in patients with severe sepsis. Whether hospitals with more experience caring for patients with severe sepsis also have improved outcomes is unclear.

Objectives: To determine associations between hospital severe sepsis caseload and outcomes.

Methods: We analyzed data from U.S. academic hospitals provided through University HealthSystem Consortium. We used University HealthSystem Consortium's sepsis mortality model (c-statistic, 0.826) for risk adjustment. Validated *International Classification of Disease, 9th Edition, Clinical Modification* algorithms were used to identify hospital severe sepsis case volume. Associations between risk-adjusted severe sepsis case volume and mortality, length of stay, and costs were analyzed using spline regression and analysis of covariance.

Measurements and Main Results: We identified 56,997 patients with severe sepsis admitted to 124 U.S. academic hospitals during 2011. Hospitals admitted 460 ± 216 patients with severe sepsis, with median length of stay 12.5 days (interquartile range, 11.1–14.2), median direct costs \$26,304 (interquartile range, \$21,900–\$32,090), and average hospital mortality $25.6 \pm 5.3\%$. Higher severe sepsis case volume was associated with lower unadjusted severe sepsis mortality ($R^2 = 0.10$, $P = 0.01$) and risk-adjusted severe sepsis mortality

($R^2 = 0.21$, $P < 0.001$). After further adjustment for geographic region, number of beds, and long-term acute care referrals, hospitals in the highest severe sepsis case volume quartile had an absolute 7% (95% confidence interval, 2.4–11.6%) lower hospital mortality than hospitals in the lowest quartile. We did not identify associations between case volume and resource use.

Conclusions: Academic hospitals with higher severe sepsis case volume have lower severe sepsis hospital mortality without higher costs.

Keywords: sepsis; outcome assessment (health care)

At a Glance Commentary

Scientific Knowledge on the Subject: In the absence of novel therapeutics, processes of care are important determinants of outcomes in patients with severe sepsis. Whether academic hospitals with more experience caring for patients with severe sepsis have better patient outcomes is currently unclear.

What This Study Adds to the Field: Academic hospitals in the United States with higher severe sepsis case volumes have lower severe sepsis case fatality rates at similar costs to low case volume hospitals.

Severe sepsis is a clinical syndrome characterized by acute organ failure resulting from the systemic immune

response to infection (1). Approximately 1 million patients in the United States are affected by severe sepsis annually (2).

Although the past 2 decades have seen a 10 to 15% absolute decline in severe sepsis case-fatality rates, patients with severe

(Received in original form November 7, 2013; accepted in final form December 31, 2013)

Supported in part by National Institutes of Health, grants NHLBI K01HL116768 (A.J.W.) and NCI K07 CA138772 (R.S.W.). R.S.W. is also supported by resources from the Edith Nourse Rodgers Memorial VA Hospital.

Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Author Contributions: A.J.W.: conception, design, acquisition of data, statistical analysis, drafting of manuscript. R.S.W.: interpretation of data, revision of article critically for intellectual content, approval of final version of the manuscript.

Correspondence and requests for reprints should be addressed to Allan J. Walkey, M.D., M.Sc.; Boston University School of Medicine; 72 East Concord Street, R-304, Boston, MA 02118. E-mail: alwalkey@bu.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 189, Iss 5, pp 548–555, Mar 1, 2014

Copyright © 2014 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201311-1967OC on January 8, 2014

Internet address: www.atsjournals.org

sepsis still suffer from 25 to 30% hospital mortality (3–7). Because improvements in severe sepsis outcomes have occurred in the absence of novel therapeutics, some have speculated that reductions in severe sepsis mortality are the result of advances in processes of care. For example, earlier administration of antibiotics (8–10), improved resuscitation techniques (11, 12), lung-protective mechanical ventilation (13), or increased availability of intensivists (14) may contribute to the increasing survival among patients with severe sepsis.

We hypothesized that centers with high severe sepsis case volume may have more effective processes of care that result in lower severe sepsis–associated hospital mortality when compared with centers with low severe sepsis case volume. Prior studies of severe sepsis volume–outcome associations outside of the United States have shown conflicting results (15–17). Detecting case volume associations for severe sepsis within the United States may have important policy implications. For example, identifying care delivery models that are associated with improved outcomes in severe sepsis may similarly enable more efficient targeting of resources to the processes or structures of care most likely to produce benefit. We sought to examine case volume–outcome associations among patients with severe sepsis admitted to U.S. academic medical centers.

Methods

We performed a retrospective cohort study of severe sepsis hospitalizations in the United States from the year 2011 using the University HealthSystem Consortium (UHC) Clinical Database Resource Manager (Chicago, IL). UHC is an alliance of approximately 90% of U.S. academic medical centers and their community hospital partners, with data contributions from 125 academic medical centers and 83 nonacademic community hospitals in 2011. UHC uses a patient-level risk-adjustment model based on severity of illness at hospital admission that includes demographics, site of referral, diagnosis, and comorbidity information to predict mortality for each patient. A standardized “mortality index” can be determined for each hospital by dividing the actual mortality (proportion of patients with severe sepsis who died) by the average of

the expected mortality for all patients treated in that hospital. A higher hospital mortality index indicates that observed mortality is greater than mortality predicted by severity of illness of the hospital case mix. The 2011 UHC hospital mortality risk adjustment model for patients with sepsis has a c-statistic of 0.826 (see Table E1 in the online supplement) (18).

We restricted our analysis to the Association of American Medical College–defined academic medical centers included in the UHC database that contributed complete data (1) because the UHC risk adjustment model is derived solely from the academic medical center members; (2) to avoid the confounding inherent in comparing larger academic hospitals to smaller nonacademic community hospitals with significantly lower case volumes; and (3) because the community hospitals often transfer the most severely ill patients to their affiliated academic medical centers, which may bias mortality estimates. We recorded hospital characteristics such as the number of hospital acute care beds, intensive care unit (ICU) structure (open vs. closed model), long-term acute care hospital (LTACH) referral practices (19), and geographic region. In addition, we collected data regarding hospital length of stay, direct costs, and mortality for all severe sepsis cases. Direct cost is an estimation of total cost using Medicare Cost Report cost-to-charge ratios after adjusting the labor portion of the costs for differences in labor costs using the area wage index and excluding overhead cost.

Severe Sepsis Case Identification

We use the term “severe sepsis” to refer to patients with severe sepsis and/or septic shock. Using previously validated algorithms, we identified adult patients aged 18 to 95 years who were hospitalized with severe sepsis. We did not limit analyses to initial severe sepsis hospitalizations. In our primary analysis we used a strategy previously described by Martin and colleagues (20) using *International Classification of Disease, 9th Edition, Clinical Modification* (ICD-9-CM) diagnosis codes for septicemia and acute organ dysfunction to identify severe sepsis in administrative data. The Martin strategy has been previously validated to have a 97% positive predictive value for severe sepsis (20) and closely approximates outcomes of

prospectively ascertained cases of severe sepsis who meet Consensus definitions (7). In our *a priori* primary analysis we included only cases with severe sepsis present on admission because (1) processes of care can differ markedly for patients admitted with severe sepsis as opposed to those who develop nosocomial sepsis, (2) ICD-9-CM codes cannot discern the temporality of the onset of infection and organ dysfunction in cases without both infection and acute organ dysfunction present on admission, and (3) the development of acute organ failure after hospital admission may partly be the result of processes of care and may confound the case volume–outcome association. We identified cases of severe sepsis that were present on admission by requiring that ICD-9-CM codes for the diagnosis of sepsis and acute organ failure were present on admission modifiers (21).

We used multiple techniques to address the possibility that hospital discharge practices may potentially bias mortality estimates if premorbid patients are differentially transferred or discharged to acute care hospitals, LTACHs, rehabilitation hospitals, or hospice facilities. First, we excluded patients transferred to another acute care hospital from all analyses. Second, we examined whether LTACH referral practices may be associated with severe sepsis mortality; noting an association, we included LTACH discharge status as a covariate in multivariable-adjusted analysis. Third, we conducted a sensitivity analysis excluding any patient not discharged to home or deceased.

Sensitivity and Subgroup Analyses

Because documentation and coding practices may vary between hospitals, we performed sensitivity analyses using alternative ICD-9-CM algorithms to identify severe sepsis in administrative data. We performed an analysis limited to severe sepsis cases identified through a more sensitive, but less specific, algorithm for severe sepsis developed by Angus and colleagues (22) that identifies severe sepsis through concomitant infection and acute organ dysfunction codes (positive predictive value, 70%) and performed a separate analysis limited to the less sensitive and more specific explicit ICD-9-CM codes for severe sepsis (995.92, 785.52, positive predictive value ~100%) (23, 24).

We performed a sensitivity analyses assessing case volume–outcome

relationship among patients admitted with severe sepsis who were managed in an ICU and also among patients requiring mechanical ventilation. We conducted a subgroup analysis stratifying severe sepsis hospitalizations by medical and surgical Medicare-Severity Diagnosis Related Group codes. For all analyses, severe sepsis case volume was defined as the number of patients with severe sepsis meeting the specific analysis criteria (ie., “Martin” algorithm, “Angus” algorithm, intensive care, mechanical ventilation) who were discharged from each hospital during the time period from January 1, 2011, to December 31, 2011.

Hospitals, rather than individual patients, were the unit of analysis. Our primary outcome was the average hospital mortality index, defined as the ratio of observed to average expected mortality derived from severe sepsis cases at each hospital. As secondary outcomes, we explored associations between severe sepsis case volume and average severe sepsis length of stay among all patients with severe sepsis and severe sepsis survivors, as well as direct costs.

Statistical Analyses

Normally distributed continuous variables are presented as means and SDs and nonnormally distributed variables as medians and interquartile ranges (IQRs). We compared differences between severe sepsis quartile groups with analysis of variance or Kruskal-Wallis testing, as appropriate.

We used two different regression methods to demonstrate the association between severe sepsis case volume and outcome. First, we used penalized B-spline regression to visually demonstrate the unadjusted association between severe sepsis case volume and severe sepsis mortality (*see the METHODS in the online supplement*) (25). Second, we used multivariable analysis of covariance models to assess the adjusted association between quartiles of severe sepsis case volume and severe sepsis mortality. Potentially confounding covariates significantly associated with either severe sepsis mortality index or with severe sepsis case volume were selected for inclusion in the multivariable-adjusted models. Variables that were not normally distributed (e.g., mortality index) were natural log-transformed for analysis of covariance

models. We report the coefficient of determination (R^2) as the proportion of between-hospital variation in severe sepsis mortality explained by severe sepsis case volume. Agreement between the different ICD-9-CM algorithms for identification of severe sepsis case volume quartiles was assessed with weighted kappa statistics (26).

We used SAS version 9.3 (Cary, NC) for all analyses and two-sided α of 0.05 as the threshold for statistical significance. Study procedures were determined to be exempt by the Boston University School of Medicine Institutional Review Board. UHC approved data presentation but had no role in planning, analysis, or authorship.

Results

Hospital and Severe Sepsis Case Characteristics

We identified 56,997 patients with severe sepsis admitted to 124 U.S. academic medical centers (Figure 1). One hospital without data available from the full year was excluded from analysis. U.S. academic hospitals averaged 591 ± 266 acute care beds and had a uniform geographic distribution. During the year 2011, U.S. academic hospitals averaged 460 ± 216 patients admitted with severe sepsis, of whom 69% required intensive care, with a median hospital length of stay of 12.5 days (IQR, 11.1–14.2), a median direct

cost of \$26,304 (IQR, \$21,900–\$32,090), and an average hospital mortality of $25.6 \pm 5.3\%$.

Characteristics of the hospitals by quartile of severe sepsis case volume are shown in Table 1. An increasing severe sepsis case volume was associated with a greater number acute care beds ($P < 0.001$). Severe sepsis case volume and severe sepsis mortality index varied by hospital geographic region ($P = 0.001$), and a greater proportion of severe sepsis cases transferred to LTACH facilities was associated with lower severe sepsis mortality index (Table E2, $P = 0.003$). Thus, geographic region, number of acute care beds, and LTACH transfer rate were included as covariates in multivariable models.

Association of Severe Sepsis Case Volume with Hospital Mortality

Increasing volume of severe sepsis cases present on admission was associated with lower hospital severe sepsis mortality index ($R^2 = 0.21$, $P < 0.001$, Figure 2A) and lower observed severe sepsis mortality ($R^2 = 0.10$, $P = 0.01$, Figure 2B) but was not associated with the expected mortality based on case-mix ($R^2 = 0.06$, $P = 0.11$, Figure 2C).

In analyses adjusted for hospital geographic region, the number of available acute care beds, and LTACH transfer rate, increasing quartiles of severe sepsis case

Figure 1. Flow diagram of hospital and severe sepsis case selection.

Table 1: Hospital and Severe Sepsis Case Characteristics

Hospital Characteristics	Severe Sepsis Case Volume Quartile (N = 31 Hospitals per Quartile)				P Value
	1 (30–317 Cases)	2 (318–437 Cases)	3 (438–603 Cases)	4 (604–977 Cases)	
Cases admitted with severe sepsis in year 2011	199 ± 79	381 ± 33	506 ± 48	752 ± 122	<0.0001
Acute care beds	336 ± 130	512 ± 173	681 ± 199	835 ± 246	<0.0001
Geographic distribution					0.001
Northeast	10 (32)	1 (3)	3 (10)	3 (10)	
Mid-Atlantic	5 (16)	9 (29)	10 (32)	3 (10)	
Southeast	5 (16)	2 (6)	6 (19)	9 (29)	
Midwest	5 (16)	7 (23)	1 (3)	10 (32)	
Mid-Central	3 (10)	3 (10)	7 (23)	4 (13)	
West	3 (10)	9 (29)	4 (13)	2 (6)	
Open intensive care unit structure (N = 105 hospitals reporting)	12 (52) (N = 23)	12 (43) (N = 28)	15 (51) (N = 29)	11 (44) (N = 25)	0.86
Characteristics of Severe Sepsis Cases					
% of severe sepsis cases requiring intensive care (N = 88 hospitals reporting)	73 ± 9 (N = 15)	71 ± 9.9 (N = 22)	69 ± 16 (N = 28)	69 ± 11 (N = 23)	0.70
% of severe sepsis cases requiring mechanical ventilation	41.5 ± 11	40 ± 10	40 ± 8.6	40 ± 7.3	0.92
% of severe sepsis cases discharged to long-term acute care hospitals	4.2 ± 5.0	3.6 ± 3.4	3.9 ± 3.8	5.0 ± 4.2	0.61
Hospital length of stay, d	12.6 (10.3–13.8)	12.4 (10.8–14.3)	12.5 (11.4–14.4)	12.6 (11.8–13.7)	0.87
Direct cost per case, 2011 U.S. \$	25,100 (17,000–3,400)	24,900 (20,300–30,500)	26,700 (23,000–34,700)	26,700 (23,300–29,300)	0.43

Data presented as mean ± SD, N (%), or median (interquartile range). P value represents comparisons between all quartiles.

volume were associated with lower mortality index (model $R^2 = 0.27$, severe sepsis case volume partial $R^2 = 0.13$, $P < 0.001$), and lower observed mortality without a significant change in expected mortality (Table 2). Compared with the lowest quartile of severe sepsis case volume, hospitals in the highest quartile had similar expected mortality but an absolute 7% (95% confidence interval [CI], 2.4–11.6%) lower risk of observed hospital mortality.

Hospital Mortality: Subgroup and Sensitivity Analyses

An analysis excluding patients discharged to any LTACH, rehabilitation hospital, or hospice facility showed associations between severe sepsis mortality index and severe sepsis case volume similar to the primary analysis ($R^2 = 0.30$, $P < 0.001$). The association of ICU sepsis case volume with the mortality index ($n = 88$ hospitals reporting, 29,662 cases, $R^2 = 0.21$, $P < 0.001$) was similar to that of the primary analysis including all hospitalized patients. The volume of severe sepsis

cases requiring mechanical ventilation was also associated with mortality index ($n = 124$ hospitals, 22,834 cases, $R^2 = 0.11$, $P = 0.005$).

Subgroup analyses stratified by medical or surgical hospitalization status showed that higher case volume of severe sepsis was associated with lower mortality index for medical hospitalizations ($n = 124$ hospitals, 45,213 cases, $R^2 = 0.23$, $P < 0.001$) but a weaker, nonsignificant association between high case volume and lower mortality for surgical hospitalizations ($n = 124$ hospitals, 11,784 cases, $R^2 = 0.07$, $P = 0.052$). Medical and surgical cases showed somewhat different patterns in the relationship between case volume and mortality measures (Table E3). For example, medical cases had lower observed mortality at high case volume, whereas expected mortality did not differ by case volume. For surgical cases, observed mortality did not differ by case volume, but expected mortality was higher at high case volume centers. On average, a greater proportion of surgical patients were transferred from other hospitals (33.8%

[95% CI, 30.2–37.4%]) than medical patients (20.0% [95% CI, 17.2–22.7%]).

Agreement between the Martin and colleagues, Angus and colleagues, and explicit ICD-9-CM codes for classification of severe sepsis case volume quartiles was substantial ($\kappa > 0.75$ for all comparisons). Severe sepsis cases identified with the Angus and colleagues algorithm identifying infection and acute organ dysfunction ($n = 124$ hospitals, $n = 105,956$, $R^2 = 0.26$, $P < 0.001$) and the explicit ICD-9-CM codes for severe sepsis ($n = 124$ hospitals, 27,743 cases, $R^2 = 0.21$, $P < 0.001$) did not yield appreciably different results from the primary analysis.

Secondary Outcomes

We found no association between severe sepsis case volume and hospital length of stay ($R^2 = 0.007$, $P = 0.93$; length of stay index $R^2 = 0.03$, $P = 0.47$) for all severe sepsis patients or for severe sepsis survivors alone (length of stay $R^2 = 0.009$, $P = 0.90$; length of stay index $R^2 = 0.038$, $P = 0.33$). Results were similar for case volume and direct costs ($n = 118$ hospitals reporting,

Figure 2. Univariate associations between severe sepsis case volume and mortality measures. (A) Association between severe sepsis case volume and hospital mortality index, $R^2 = 0.21$, $P < 0.001$. (B) Association between severe sepsis case volume and observed hospital mortality, $R^2 = 0.10$, $P = 0.01$. (C) Association between severe sepsis case volume and expected (predicted) mortality, $R^2 = 0.06$, $P = 0.11$.

54,795 cases, $R^2 = 0.007$, $P = 0.93$) or direct cost index ($R^2 = 0.01$, $P = 0.79$) among patients with severe sepsis.

Discussion

We identified a strong case volume and outcome association for severe sepsis cases admitted to U.S. academic hospitals. After adjustment for patient and hospital characteristics, the number of severe sepsis cases admitted to a hospital accounted for 13% of the adjusted between-hospital variation in severe sepsis mortality rates. Patients admitted to high severe sepsis case volume hospitals had a 7% absolute lower risk of in-hospital mortality than those admitted to low case volume hospitals. We did not identify associations between higher case volume and increased lengths of stay or costs of care for patients with severe sepsis.

Consistent evidence supporting volume–outcome associations is lacking for patients hospitalized with medical conditions not typically associated with procedures (27, 28), including studies of ICU case volume for severe sepsis in Finland (17), the UK (16), and the Netherlands (15) that have shown mixed results. Direct comparisons between the severe sepsis case volume–outcome experience outside the United States and our data from the United States are challenging for a number of reasons. For example, delivery of critical care services varies substantially between countries (29); it is possible that some systems of care are more sensitive to volume–outcome associations than others. In addition, we present data for hospital-level case volume, rather than ICU-level case volume shown in prior studies. Because patients with severe sepsis are often provided care across a spectrum of clinical settings during a single hospitalization (e.g., emergency department, intensive care, ward), hospital-level data may be more sensitive to detect volume–outcome associations than data from individual ICUs. A prior study in the United States identified a case volume–outcome association for patients admitted through an emergency department who had a principal diagnosis of sepsis (30) but was unable to identify cases with severe sepsis, evaluate the temporality of sepsis diagnoses, or adjust for differences in severity of case mix. Further study of volume–outcome

Table 2: Measures of Hospital Mortality and Severe Sepsis Case Volume

Hospital Mortality Measure	Severe Sepsis Case Volume Quartile			
	1 (30–317 Cases)	2 (318–437 Cases)	3 (438–603 Cases)	4 (604–977 Cases)
Observed mortality				
Unadjusted	27.3 (25.2–29.5)	25.4 (23.4–27.4)	26.4 (24.8–28.0)	23.3 (21.4–25.2)*
Adjusted [†]	29.2 (27.0–31.4)	26.1 (24.2–28.0)	25.0 (23.1–26.8)*	22.2 (20.1–24.3) [‡]
Expected mortality				
Unadjusted	22.8 (21.5–24.1)	23.0 (22.1–23.9)	24.3 (23.3–25.2)	24.2 (23.1–25.2)
Adjusted [†]	23.5 (22.2–24.8)	23.0 (21.9–24.1)	24.1 (23.0–25.2)	23.5 (22.2–24.8)
Mortality index [§]				
Unadjusted	1.19 (1.09–1.30)	1.08 (1.00–1.17)	1.08 (1.02–1.14)	0.95 (0.88–1.01) ^{,†}
Adjusted [†]	1.24 (1.14–1.34)	1.12 (1.05–1.20)	1.02 (0.96–1.09) [‡]	0.93 (0.86–1.00) ^{,**}

Data are presented as % (95% confidence interval).

*Statistically significant from quartile 1, $P < 0.05$.

[†]Adjusted for number of acute care beds, hospital region, and proportion of severe sepsis cases transferred to long-term acute care hospitals.

[‡]Statistically significant from quartile 1, $P < 0.01$.

[§]Value is the geometric mean.

^{||}Statistically significant from quartile 1, $P < 0.0001$.

^{††}Statistically significant from quartile 2, $P < 0.05$.

^{**}Statistically significant from quartile 2, $P < 0.01$.

associations across differing within-hospital care units may help to pinpoint processes most susceptible to variations in case volume.

Similar volume–outcome associations have been identified for critical care procedures such as mechanical ventilation (31, 32). However, because only 40% of patients with severe sepsis received mechanical ventilation, and the association between case volume and mortality was more modest among severe sepsis cases requiring mechanical ventilation, it is unlikely that mechanical ventilation case volume alone fully accounts for our findings.

We did not identify as strong a case volume–outcome association for surgical patients with severe sepsis ($R^2 = 0.07$, $P = 0.052$) as in medical patients ($R^2 = 0.23$, $P < 0.001$). This finding differs from a prior report from Finland describing a stronger case–volume association for surgical patients than medical patients (17). The lack of a statistically significant association between case volume and outcomes for patients with severe sepsis requiring surgery may have several explanations. The volume of surgical patients with severe sepsis was markedly lower (25%) than that of the medical patients; separation in outcome by case volume may be more difficult to detect

among substantially fewer surgical patients. In addition, surgical patients with severe sepsis cared for at high-volume U.S. centers appeared to have higher severity of illness, with higher expected mortality rates, when compared with surgical patients with severe sepsis at low-volume centers. Furthermore, a greater proportion of surgical patients with severe sepsis were admitted via transfer from other hospitals than medical patients with severe sepsis. Thus, the flow of surgical patients with severe sepsis between U.S. centers appears more complex than that of the medical patients, a process that may impair our ability to detect case–volume associations in these patients.

We found evidence of variation in severe sepsis mortality by geographic region. Prior studies have shown that practice patterns for patients with severe sepsis vary significantly by geography; for example, fewer patients in the Northeast received central venous pressure monitoring than in other regions (33). Further studies should explore other potential reasons for the association between geographic region and severe sepsis mortality.

Case volume and outcome associations have been well described for high-risk, semielective surgical procedures (34–36), resulting in policy recommendations for minimum case volume rates necessary to

perform high-risk cancer surgery (37). Implementation of recommendations to increase the centralization of high-risk surgeries was associated with improved mortality (38, 39). Our results may at first glance appear to argue for similar centralization of care for severe sepsis. For example, approximately 40% of severe sepsis cases are transported via prehospital emergency medical service providers that potentially could recognize and selectively triage patients with severe sepsis to high-volume centers (21). However, such policy shifts would require substantial infrastructure changes for acutely ill patients with severe sepsis, as compared with patient scheduling for semielective high-risk cancer surgery. Bypassing local centers with lower case volume to regionalize patients with severe sepsis to high-volume centers may be unrealistic and counterproductive, potentially increasing the time to first antibiotic dose and resulting in worse outcomes (10–12). In addition, by further depleting low-volume centers of experience caring for patients with severe sepsis, outcomes of patients developing nosocomial sepsis at the low-volume centers may deteriorate. Additional studies using simulation modeling or operations research methodologies may advance our understanding of the net effects severe sepsis care regionalization may have on patient outcomes (40).

An alternative solution to decrease disparities in outcomes based on case volume may be to determine the processes and structures of care delivery at high-volume severe sepsis centers that are important determinants of outcome and translate these effective processes to lower volume or lower performing centers. Thus, further studies using alternative data sources are needed to determine whether processes of care, such as use of protocols (41), time to effective antibiotics (10–12), early central venous catheter placement (12) for implementation of early goal-directed therapy (11), or use of lung-protective ventilation (13, 32), are performed to a greater extent in high-volume, high-performing centers.

Strengths of our study include the ability to adjust for variable clinical case mix using a validated risk-adjustment model, restriction to academic centers to reduce confounding by teaching hospital status, use of the hospital as the unit of

analysis, and consistency of the results across multiple sensitivity analyses to address potential differences in hospital-level ICD-9-CM coding practices and discharge practices. Limitations of our study include use of retrospective administrative data without individual physiological variables that would allow use of other ICU-specific methods to adjust for severity of illness (e.g., Acute Physiology and Chronic Health Evaluation scores), detailed information regarding individual patient or hospital structural factors (e.g., number of ICU beds) that may contribute to residual

confounding, as well as limited generalizability outside of U.S. academic hospitals.

In conclusion, we found that patients with severe sepsis who are cared for at U.S. academic medical centers with a higher severe sepsis case load have lower risk-adjusted hospital mortality. Absolute risk of hospital death was 7% lower among patients admitted to hospitals with the highest severe sepsis volume when compared with lowest-volume hospitals, without differences in costs. Further studies that seek to determine the specific structures and processes of care

associated with improved outcomes at the high-volume hospitals are needed to reduce the disparities in severe sepsis outcomes at lower severe sepsis case volume centers. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The information contained in this article was based in part on the Clinical Database/Resource Manager (CDB/RM) maintained by the University HealthSystem Consortium (UHC). The authors thank Samuel Hohmann, Ph.D., Principal Consultant at UHC, for his assistance.

References

- Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ; The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644–1655.
- HCUPnet. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. 2011 [accessed 2013 Jun 3]. Available from: <http://hcupnet.ahrq.gov>
- Kumar G, Kumar N, Taneja A, Kaleelal T, Tarima S, McGinley E, Jimenez E, Mohan A, Khan RA, Whittle J, et al.; Milwaukee Initiative in Critical Care Outcomes Research Group of Investigators. Nationwide trends of severe sepsis in the 21st century (2000–2007). *Chest* 2011;140:1223–1231.
- Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. *J Am Geriatr Soc* 2012;60:1070–1077.
- Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care* 2006;10:R42.
- ARISE; ANZICS APD Management Committee. The outcome of patients with sepsis and septic shock presenting to emergency departments in Australia and New Zealand. *Crit Care Resusc* 2007;9:8–18.
- Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. *Crit Care Med* [online ahead of print] 6 Nov 2013; DOI: 10.1097/CCM.0000000000000026.
- Kumar A, Haery C, Paladugu B, Kumar A, Symeonides S, Taiberg L, Osman J, Trenholme G, Opal SM, Goldfarb R, et al. The duration of hypotension before the initiation of antibiotic treatment is a critical determinant of survival in a murine model of *Escherichia coli* septic shock: association with serum lactate and inflammatory cytokine levels. *J Infect Dis* 2006;193:251–258.
- Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, et al.; Surviving Sepsis Campaign. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010;38:367–374.
- Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589–1596.
- Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–1377.
- Walkey AJ, Wiener RS, Lindenauer PK. Utilization patterns and outcomes associated with central venous catheter in septic shock: a population-based study. *Crit Care Med* 2013;41:1450–1457.
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
- Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA* 2002;288:2151–2162.
- Peelen L, de Keizer NF, Peek N, Scheffer GJ, van der Voort PH, de Jonge E. The influence of volume and intensive care unit organization on hospital mortality in patients admitted with severe sepsis: a retrospective multicentre cohort study. *Crit Care* 2007;11:R40.
- Shahin J, Harrison DA, Rowan KM. Relation between volume and outcome for patients with severe sepsis in United Kingdom: retrospective cohort study. *BMJ* 2012;344:e3394.
- Reinikainen M, Karlsson S, Varpula T, Parviainen I, Ruokonen E, Varpula M, Ala-Kokko T, Pettilä V. Are small hospitals with small intensive care units able to treat patients with severe sepsis? *Intensive Care Med* 2010;36:673–679.
- UHC. Risk adjustment methodology for 2011 database [accessed 2013 Jun 3]. Available from: <https://www.uhc.edu>
- Hall WB, Willis LE, Medvedev S, Carson SS. The implications of long-term acute care hospital transfer practices for measures of in-hospital mortality and length of stay. *Am J Respir Crit Care Med* 2012;185:53–57.
- Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–1554.
- Seymour CW, Rea TD, Kahn JM, Walkey AJ, Yealy DM, Angus DC. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. *Am J Respir Crit Care Med* 2012;186:1264–1271.
- 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;29:1303–1310.
- Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011;306:2248–2254.
- Iwashyna TJ, Odden A, Rohde J, Bonham C, Kuhn L, Malani P, Chen L, Flanders S. Identifying patients with severe sepsis using administrative claims: patient-level validation of the Angus implementation of the International Consensus Conference Definition of Severe Sepsis. *Med Care* [online ahead of print] 18 Sep 2012; DOI: 10.1097/MLR.0b013e318268ac86.

25. Eilers PHC, Marx BD. Flexible smoothing with B-Splines and penalties. *Stat Sci* 1996;11:89–121.
26. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–174.
27. Lindenauer PK, Behal R, Murray CK, Nsa W, Houck PM, Bratzler DW. Volume, quality of care, and outcome in pneumonia. *Ann Intern Med* 2006;144:262–269.
28. Lin HC, Xirasagar S, Chen CH, Hwang YT. Physician's case volume of intensive care unit pneumonia admissions and in-hospital mortality. *Am J Respir Crit Care Med* 2008;177:989–994.
29. Wunsch H, Angus DC, Harrison DA, Collange O, Fowler R, Hoste EA, de Keizer NF, Kersten A, Linde-Zwirble WT, Sandiumenge A, Rowan KM. Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008;36:2787–2793.e1–9.
30. Powell ES, Khare RK, Courtney DM, Feinglass J. Volume of emergency department admissions for sepsis is related to inpatient mortality: results of a nationwide cross-sectional analysis. *Crit Care Med* 2010;38:2161–2168.
31. Kahn JM, Ten Have TR, Iwashyna TJ. The relationship between hospital volume and mortality in mechanical ventilation: an instrumental variable analysis. *Health Serv Res* 2009;44:862–879.
32. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med* 2006;355:41–50.
33. Lagu T, Rothberg MB, Nathanson BH, Pekow PS, Steingrub JS, Lindenauer PK. Variation in the care of septic shock: the impact of patient and hospital characteristics. *J Crit Care* 2012;27:329–336.
34. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;349:2117–2127.
35. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med* 1979;301:1364–1369.
36. Wouters MW, Gooiker GA, van Sandick JW, Tollenaar RA. The volume-outcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. *Cancer* 2012;118:1754–1763.
37. Milstein A, Galvin RS, Delbanco SF, Salber P, Buck CR Jr. Improving the safety of health care: the leapfrog initiative. *Eff Clin Pract* 2000;3:313–316.
38. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011;364:2128–2137.
39. de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH, Porte RJ, Gouma DJ, Busch OR, Molenaar IQ; Dutch Pancreatic Cancer Group. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *Br J Surg* 2012;99:404–410.
40. Noonan VK, Soril L, Atkins D, Lewis R, Santos A, Fehlings MG, Burns AS, Singh A, Dvorak MF. The application of operations research methodologies to the delivery of care model for traumatic spinal cord injury: the access to care and timing project. *J Neurotrauma* 2012;29:2272–2282.
41. Checkley W, Martin GS, Brown SM, Chang SY, Dabbagh O, Fremont RD, Girard TD, Rice TW, Howell MD, Johnson SB, *et al.*; United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study Investigators. Structure, process, and annual ICU mortality across 69 centers: United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study. *Crit Care Med* 2014;42:344–356.