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Did They Just Prove That a Diagnosis of "Septic Shock" Is Meaningless?

Annane and colleagues' oft-cited 2005 review of septic shock in *The Lancet* features a lovely set of graphics (1). In their Figure 1, there is a small oval at the top labeled "Bacteria." This generic infection triggers at least eight separately identified effector pathways, which ramify out to show the multiple systems that lead "from bacteria to disease." In their Figure 2, dozens of intracellular interactions are laid out, but the only vestige of the bacteria is an extracellular lipopolysaccharide. By 2013, Figure 1 of Angus and van der Poll's *NEJM* review is entirely about the "Host Response in Severe Sepsis"—the pathogens are nearly invisible (2). In this understanding of severe sepsis, the story is about the host response, particularly the dysregulated inflammatory and coagulopathic cascades. Pathogens enter only to the extent that they create physiologically interesting molecular patterns that trigger this host response.

In this issue of the *Journal* (pp. 1204–1213), the Co-operative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group, led by Dr. Leligdowicz, seeks to inject a note of discord into this perspective (3). This is a group well known to intensive care unit practitioners and researchers alike—the group whence our best evidence for the critical importance of time to antibiotics in septic shock came (4). In an expanded database, the authors now ask, are all infections really the same once they produce septic shock?

Leligdowicz and colleagues suggest there are important differences within septic shock. The group examined a cohort of nearly 8,000 patients diagnosed with septic shock. They found that there was clinically meaningful and statistically significant variation in hospital mortality as a function of the source of infection. Adjusted mortality varied among sites from about one-third (diverticulitis and obstruction-related urinary tract infection) to nearly three-fourths (several abdominal infections). This variation persisted after adjusting for a multitude of predisposing and downstream factors, including year of admission, demographics, 12 comorbidities, and even Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The authors suggest that we should take into account sources of infection so that patients are appropriately risk stratified and all potential factors impacting mortality are evaluated for interventions.

The authors have shown that there are crucial differences in short-term outcomes by source of infection in patients with septic shock. Have they thereby proven the "host response" consensus to be wrong? More generally, have they shown that our current understanding of "sepsis" as a meaningful diagnosis is too severe an oversimplification?

These questions hinge on what exactly we want from a diagnosis. The conflict over the Berlin definition of acute respiratory distress syndrome may be interpreted in a similar light (5, 6). It may be, we would like to suggest, that we want too many things from a single diagnosis—even a disease diagnosis, let alone an admittedly "syndromic" diagnosis (*see* Table 1).

For some situations, particularly those of research, a diagnosis should be straightforward: it is a clinical representation of a unique pathological disturbance. What we want from a diagnosis is to define a sufficiently homogenous clinical entity for which we can work to identify the specific mechanism that produces said

Table 1: The Uses of Diagnosis

• Identify patients with a single underlying pathology and mechanism of disease
• Identify patients who will respond to a given therapeutic regime
• Facilitate meaningfully precise prognostication to guide informed decision making
• Facilitate prediction of natural history to determine if alternative diagnostic work-up is necessary
• Reduce cognitive complexity for clinicians and simplify data
• Support effective communication with other clinicians for care coordination

Note that the importance of any given use will vary across situations, and that these uses have only incomplete alignment.

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diagnosis. Such an understanding of diagnosis is particularly useful for driving forward animal-based research and ensuring close correlations between animal and human models of a condition.

In contrast, at other times, the point of making a diagnosis is that it allows one to bring treatment to bear. Distinctions in diagnosis that do not lead to differences in treatment may be intellectually intriguing, but are thought to be of no clinical consequence. The art of diagnosis is then the art of matching efficacious treatments to the patients who will benefit from those interventions.

In still other situations, we want a diagnosis to imply a coherent natural history and predictable course. A diagnosis that implies too wide an array of outcomes can lead to little informed patient decision making. In the long term, such a diagnosis implies the need to simply wait and see. In the short term, such variability precludes the ability to detect when things are going off track, or even when a second look is necessary to reconsider an alternative diagnosis. From this prognostic standpoint, consistency of future course is the key requirement for a workable diagnosis.

Finally, sometimes the point of a diagnosis is communication—with ourselves and with other clinicians. A diagnosis is a cognitive shorthand that lets us reduce the complexity of an individual's story into an archetype so we can remember what is going on with that patient and share that understanding with others to coordinate care.

In an ideal world, these different desires would all point in one direction. In the real world, there is at best a loose coupling between any of these. Dr. Leligdowicz and colleagues' work certainly suggests that septic shock, as currently implemented, fails to meet the coherent natural history standard. This is true at least for short-term mortality, and we can only speculate about longer-term patient-centered outcomes. Such heterogeneity implies concerns about a host of dependent issues, including unmeasured heterogeneity in clinical trials and insufficient risk adjustment in current severity of illness scores that lump everything together as "septic shock." These findings also imply that there is important work to be done in understanding the variation in host response between sources of infection, and in finding practical ways to get all abdominal infections to behave more likely diverticulitis. This article may suggest that insufficient attention is being devoted to source-specific treatment investigations.

In the meantime, septic shock remains a pragmatically useful organizing concept—although perhaps more like "cancer" than "HER2/neu–overexpressing stage IIA breast cancer." Our resuscitations are still usefully guided by a notion of septic shock while we complete our efforts at source control (7, 8). Long-term outcome studies have not yet shown meaningful differences in outcomes across sites of infection, although existing efforts were underpowered to rule out such a possibility (9). The urgent challenge remains to integrate epidemiologic insights such as those from the current article into clinically relevant animal models and treatment trials. Dr. Leligdowicz and colleagues suggest there may be great benefits from bringing the source of the infection back into the forefront of septic shock research. ■

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Antibiotics Might Do More Than Cause Resistance

Antibiotics have revolutionized medicine, and the success of many modern treatment approaches, such as transplantation, prolonged and intensive immunosuppression, and treatment in intensive care units (ICUs), would be significantly reduced without these miracle drugs. Yet, the use of antibiotics comes at a price, which is the selection of antibiotic resistance. This natural process in bacteria in

ORIGINAL ARTICLE

Association between Source of Infection and Hospital Mortality in Patients Who Have Septic Shock

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Abstract

Rationale: Mortality caused by septic shock may be determined by a systemic inflammatory response, independent of the inciting infection, but it may also be influenced by the anatomic source of infection.

Objectives: To determine the association between the anatomic source of infection and hospital mortality in critically ill patients who have septic shock.

Methods: This was a retrospective, multicenter cohort study of 7,974 patients who had septic shock in 29 academic and community intensive care units in Canada, the United States, and Saudi Arabia from January 1989 to May 2008.

Measurements and Main Results: Subjects were assigned 1 of 20 anatomic sources of infection based on clinical diagnosis and/or isolation of pathogens. The primary outcome was hospital mortality. Overall crude hospital mortality was 52% (21–85% across sources of infection). Variation in mortality remained after adjusting for year of admission, geographic source of admission, age, sex, comorbidities, community- versus hospital-acquired infection, and organism type. The source of infection with the highest standardized hospital mortality was ischemic bowel (75%); the lowest was obstructive uropathy–associated urinary tract infection (26%). Residual variation in adjusted hospital mortality was not explained by Acute Physiology and Chronic Health Evaluation II score, number of Day 1 organ failures, bacteremia, appropriateness of empiric antimicrobials, or adjunct therapies. In patients who received appropriate antimicrobials after onset of hypotension, source of infection was associated with death after adjustment for both predisposing and downstream factors.

Conclusions: Anatomic source of infection should be considered in future trial designs and analyses, and in development of prognostic scoring systems.

Keywords: septic shock, pathogenesis; hospital mortality

At a Glance Commentary

Scientific Knowledge on the Subject: The independent role of the anatomic site of infection in mortality caused by septic shock has been addressed in previous discordant studies that varied in sample size, time point of data collection, method of analysis, and adjustment variables.

What This Study Adds to the Field: In this study of a large database that included consistent timing of data collection, appropriate time-to-event analysis, and extensive adjustment, we found variation in hospital mortality by anatomic source of infection. Therefore, anatomic source of infection should be considered explicitly in future data analyses and trial designs, and in development of new prognostic scoring systems for patients who have septic shock.

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Introduction of guidelines and application of proven treatments (1–10) have contributed to decreasing mortality of patients who have severe sepsis and septic shock (11–17). Although current knowledge suggests that the primary driver of mortality in septic shock is the systemic inflammatory response, the trigger of this response is uncontrolled infection arising from a specific anatomic source. Therefore, anatomic source of infection may influence the progression and clinical outcome of septic shock.

The independent role of the anatomic site of infection in mortality caused by septic shock has been addressed in previous discordant studies (18–20). These studies varied in sample size, time point of data collection, method of analysis, and adjustment variables. Furthermore, time to the initiation of antimicrobials after the onset of hypotension (4) was not considered as an explanatory factor. We hypothesized that even after appropriate adjustment, variation in hospital mortality caused by septic shock is explained in part by anatomic source of infection.

The primary aim of this retrospective observational study was to describe variation in hospital mortality across anatomic sources of infection after adjustment for predisposing factors (year of septic shock, source of admission, age, sex, comorbidities, community- vs. hospital-acquired infection, and organism type) and to determine if factors known after admission to intensive care unit (ICU) (Acute Physiology and Chronic Health Evaluation [APACHE] II score, number of Day 1 organ failures, bacteremia and fungemia [presence of positive blood cultures for a pathogen], appropriateness of antimicrobial agents, use of adjunct therapy, and timing of initiation of antimicrobial agents after the onset of hypotension) explain residual variation in mortality. Some of the results of this study have been previously reported in the form of an abstract (21).

Methods

This retrospective observational cohort study included consecutive adult patients (≥18 yr old) who were admitted because of septic shock to the ICUs in 29 academic and community hospitals in Canada (n = 22), United States (n = 6), and Saudi Arabia (n = 1). Data were collected in periods for each hospital between January 1989 and May 2008. These centers were contributors to the Cooperative Antimicrobial Therapy of Septic Shock Database. Septic shock was defined according to the Society of Critical Care Medicine/American College of Chest Physicians consensus statement of sepsis definitions (22). All patients included in the database had a first-time diagnosis of septic shock during the current hospitalization and had no other obvious cause of shock. The study was approved by the Health Ethics Board of the University of Manitoba and the Research Ethics Board of each participating center.

Data Elements and Definitions

Definitions of clinical infection have been described previously (4). Briefly, pathogens that were potential causes of septic shock had to be isolated from the local site and/or blood cultures that were obtained within 48 hours of onset of shock. *A priori* criteria were developed to determine the primary pathogens and to assess the appropriateness of antimicrobial therapy across participating institutions (4, 23). Patients were assigned to 1 of 20 primary anatomic sources of infection based on clinical diagnosis and/or isolation of pathogens. These anatomic sources were intraabdominal infection subdivided into nine common clinical syndromes (cholecystitis and cholangitis, peritonitis/abscess/small bowel obstruction, spontaneous bacterial peritonitis, *Clostridium difficile*–associated colitis, perforated viscus, enterocolitis and diverticulits, ischemic bowel, pancreatitis, other), genitourinary subdivided into pyelonephritis and obstructive uropathy–associated urinary tract infection, and skin and soft tissue infection subdivided into cellulitis/abscess/necrotizing fasciitis/decubitus ulcer and bone and joint infection.

The time of initiation of appropriate antimicrobial therapy after the onset of hypotension was determined according to established definitions (23). Appropriate therapy was defined as an antimicrobial agent that had *in vitro* microbiologic activity against the isolated pathogen (or if no organism was isolated, appropriate for the underlying clinical syndrome). Appropriate empiric therapy for culture-negative infections was defined by the recommendations from the *Sanford Guide to Antimicrobial Therapy 2004* (34th edition) (24).

Data were collected by trained research nurses and medical students using a standardized and piloted data form. Variables collected included predisposing factors and downstream factors. The predisposing factors included year of admission for septic shock, patient demographics (age, sex), source of admission (emergency department, surgical ward, medicine ward), baseline comorbidities (AIDS, leukemia, lymphoma, metastatic cancer, liver failure, hypertension, heart failure, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, dialysis, diabetes mellitus, surgery, alcohol abuse, intravenous drug use, cerebrovascular accident, and neurologic disease), community- versus hospital-acquired infection, and organism type (culture-negative, gram-positive bacteria, gram-negative bacteria, anaerobes, and other including fungi and *Mycobacterium tuberculosis*). Downstream factors included APACHE II score during the first 24 hours after onset of shock (25), number of Day 1 organ failures (4), bacteremia and fungemia, appropriateness of antimicrobial agents, and adjunct therapy (glucocorticoids, activated protein C). Predisposing factors were defined as variables measured before ICU admission and not a result of management of septic shock. Downstream factors were defined as variables measured after admission to ICU and could be related to the natural history and/or management of septic shock. Cases obtained at hospital sites where only septic shock cases caused by *Candida* infection were collected (for a related study) were excluded to avoid skewing the analysis. Questionable cases or data elements were adjudicated by the principal investigator.

Statistical Analysis

The primary outcome variable was survival to hospital discharge, including discharge to a chronic healthcare facility. This outcome was selected over 28-day mortality because late sequelae from septic shock are not captured by 28-day mortality and many patients are still in-hospital at Day 28 (26). Crude hospital mortality was calculated for groups according to anatomic source of

infection. To determine the variation in mortality across anatomic sources of infection after accounting for differences in underlying patient characteristics, a generalized estimating equations logistic regression model with clustering of patients by hospital site was fit. The first model included only predisposing factors as adjustment variables. A second model that included both predisposing factors and downstream clinical and metabolic response factors was fit to explore the extent to which remaining variation in mortality might be explained by factors downstream from ICU admission. The null hypothesis that mortality does not differ across infection sources was assessed using the Wald test.

Because the timing of initiation of appropriate antimicrobials has been shown to impact hospital survival (4), Cox proportional hazards modeling (with patient clustering by hospital site) was used to assess how much variability in the time to death was explained by predisposing, and predisposing plus downstream factors, including the timing of initiating appropriate antimicrobials after onset of hypotension among the subgroup of patients who received appropriate antimicrobial agents after the onset of hypotension. Initiation of antimicrobial agents was entered as a time-dependent explanatory variable. In these models, follow-up was censored at hospital discharge for those patients who survived their hospital stay.

To better understand the absolute magnitude and facilitate comparison of the mortalities across sources of infection, standardized mortalities were calculated based on the logistic regression models using the characteristics of the patient sample as the reference distribution. That is, for each source of infection, the standardized mortality was obtained by averaging across all patients the predicted risks of death obtained under the assumption that each patient had this anatomic source of infection. This analysis was also done for the proportional hazards models, using predicted mortality at 28th day of follow-up as the parameter of interest.

In sensitivity analyses we examined the same four regression models stratified by categories of culture results for the responsible pathogen: gram-positive bacteria, gram-negative bacteria, culture-negative, *Staphylococcus aureus* (the most common gram-positive pathogen in our series), and *Escherichia coli* (the most common gram-negative pathogen in our series). Anatomic sites were included in these models if at least 20 patients were present in each of the five culture categories for a given anatomic site.

In all statistical models, the lung was used as the reference anatomic source of infection because it was the most common anatomic source of infection. Statistical analyses were done using Statistical Analysis Software (version 9.3; SAS Institute, Inc., Cary, NC) and R (version i386 3.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and Descriptive Data

Of 8,670 eligible patients in the database, 696 were excluded because they were obtained at hospital sites where only cases caused by *Candida* were collected. Therefore, 7,974 consecutive patients in the database met the diagnostic criteria for septic shock and were potentially eligible for inclusion in the analysis (Table 1). The mean age of patients was 63 years and 57% were males. The median APACHE II score was 25 (interquartile range, 20–31). Community-acquired infections accounted for 61% of the cases of septic shock and 37% of the patients were admitted to the ICU directly from the emergency

Table 1: Characteristics of Patients

	N
All patients	7,974
Predisposing factors	
Source of admission, n (%)	
Emergency room	3,001 (37.6)
Medicine ward	2,489 (31.2)
Surgical ward	1,273 (16)
Transfer from another hospital	1,211 (15.2)
Age, mean (±SD)	63 (16)
Sex, male (%)	4,543 (57.0)
Comorbidities, n (%)	
HIV/AIDS	217 (2.7)
Lymphoma/leukemia	679 (8.5)
Metastatic cancer	730 (9.2)
Transplant	360 (4.5)
Liver failure	582 (7.3)
HTN/CHF/CAD	2,621 (32.9)
Chronic obstructive pulmonary disease	1,173 (14.7)
Chronic kidney disease	593 (7.4)
Dialysis	590 (7.4)
Diabetes	2,079 (26.1)
Surgery	1,697 (21.3)
Alcohol/intravenous drug use	1,149 (14.4)
CVA/neurologic disease	547 (6.9)
Community vs. hospital acquired, n (%)	4,822 (60.5)
Organism type, n (%)	
Gram-positive	2,731 (34.2)
Gram-negative	2,053 (25.7)
Anaerobes	274 (3.4)
Other	448 (5.6)
Culture-negative	2,468 (31.0)
Downstream factors	
APACHE-II, median (IQR)	25 (20–31)
# of Day 1 organ failures, median (IQR)	4 (3–5)
Bacteremia, n (%)	2,598 (32.6)
Appropriate antibiotics, n (%)	1,370 (17.2)
Adjunct therapy, n (%)	
Steroids	2,466 (30.9)
Activated protein C	351 (4.4)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; HTN = hypertension; IQR = interquartile range.

department. Infection was documented by a positive culture in 69% of patients; the remainder had no positive cultures but had definitive radiologic, surgical, autopsy, or biopsy evidence of infection. Of those who had positive cultures, gram-negative organisms accounted for 50%, gram-positive organisms for 37%, anaerobic organisms for 5%, and fungi (mostly *Candida*) and *M. tuberculosis* for 8%. Blood cultures were positive in 33% of the patients (Table 1). The most common anatomic source of infection was lung (40%), followed by intraabdominal (31% across all subsites) and genitourinary tract (11% including pyelonephritis and obstructive uropathy–associated urinary tract infection) (Table 2). Of the 5,782 patients who did not receive antimicrobial agents before the onset of hypotension, 323 never received appropriate antimicrobials.

Overall crude hospital mortality was 52% and ranged from 21 to 85% across sources of infection (Table 2). The crude hospital mortality for those patients in whom lung was the anatomic source of infection was 54%. Enterocolitis and diverticulitis, obstructive uropathy–associated urinary tract infection, and pyelonephritis were the anatomic sources of infection associated with the lowest crude hospital mortality. Disseminated infections (primarily *Candida* isolated at multiple sites), ischemic bowel, and spontaneous bacterial peritonitis were the sources of infection associated with the highest crude mortality.

Variation in Hospital Mortality by Anatomic Source of Infection after Adjusting for Predisposing and Downstream Factors

After adjusting for the predisposing factors, variation in hospital mortality across sources of infection remained largely unchanged from the level seen for crude hospital mortality (Figure 1A) and was statistically significant (Wald chi-square statistic = 118,282; $df = 7$; $P < 0.0001$). The addition of downstream factors to the model resulted in minimal further change to the odds ratios (Figure 1B). Figure 2 shows the crude and standardized hospital mortalities after adjustments. Adjustment for predisposing factors affected the estimated mortality for several sources of infection. In particular, the estimated hospital mortality in the disseminated infection and spontaneous bacterial peritonitis groups decreased by 21% and 19%, respectively, whereas mortality in the central nervous system infection group increased by 16%. However, substantial variation remained and standardized hospital mortalities ranged from 28% to 75%. Although the ranking of the anatomic sources of infection was affected by adjustment, the groups near the extremes of the range of mortality were similar to the ones seen in the crude analysis. The anatomic sources of infection associated with the highest hospital mortality were disseminated infection and intraabdominal infection secondary to ischemic bowel, whereas the sources associated with the lowest hospital mortality were obstructive uropathy–associated urinary tract infection and intraabdominal infection secondary to enterocolitis and diverticulitis. The addition of downstream factors to the model did not explain the residual variation in mortality across sources of infection in the first adjusted model and was associated with minimal changes in the standardized hospital mortalities (Figure 2).

Variation in Time to Death in Hospital by Anatomic Source of Infection after Adjusting for Predisposing and Downstream Factors

In the subgroup of patients (n = 5,782) in whom appropriate antimicrobial agents were administered after the onset of hypotension, variation in the risk of death across anatomic sources of infection was reduced after adjustment for predisposing factors but substantial variation remained (Figure 3A). Addition of downstream factors in the model, including time from

Table 2: Cohort Characteristics by Anatomic Source of Infection

Infection Source	N (%)	Mean Age (±SD)	Median APACHE II (IQR)	Crude Hospital Mortality (%)
All patients	7,974	63 (16)	25 (20–31)	52.4
Lung	3,196 (40.1)	62 (17)	25 (20–31)	54.0
Perforated viscus	753 (9.4)	68 (15)	24 (19–30)	55.6
Ischemic bowel	425 (5.3)	69 (13)	28 (22–34)	77.9
Cholecystitis/cholangitis	332 (4.2)	69 (14)	23 (18–29)	38.3
Peritonitis/abscess/small bowel obstruction	298 (3.7)	65 (15)	24 (18–30)	54.0
Clostridium difficile–associated colitis	211 (2.6)	64 (17)	28 (22–32)	68.3
Spontaneous bacterial peritonitis	157 (2.0)	56 (14)	28 (23–35)	76.4
Pancreatitis	86 (1.1)	60 (15)	24 (18–30)	50.0
Other intraabdominal infection	36 (0.5)	61 (16)	20 (16–25)	66.7
Enterocolitis/diverticulitis	25 (0.3)	66 (14)	22 (18–28)	28.0
Pyelonephritis	747 (9.4)	66 (15)	24 (19–29)	34.1
OU-UTI	95 (1.2)	65 (14)	22 (17–28)	21.1
Cellulitis/abscess/NecFas/decubitus ulcer	552 (6.9)	60 (15)	23 (18–30)	42.0
Bone/joint	61 (0.8)	63 (15)	27 (23–33)	52.5
Surgical site infection	90 (1.1)	64 (13)	21 (18–28)	43.3
Primary bloodstream infection	397 (5.0)	56 (16)	27 (23–33)	59.5
Intravascular catheter	257 (3.2)	58 (15)	25 (20–31)	41.3
Disseminated infection	116 (1.5)	55 (16)	28 (22–33)	84.5
Central nervous system infection	67 (0.8)	49 (21)	24 (19–29)	44.8
Other	73 (0.9)	56 (21)	21 (17–28)	38.4

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; NecFas = necrotizing fasciitis; OU-UTI = obstructive uropathy–associated urinary tract infection.

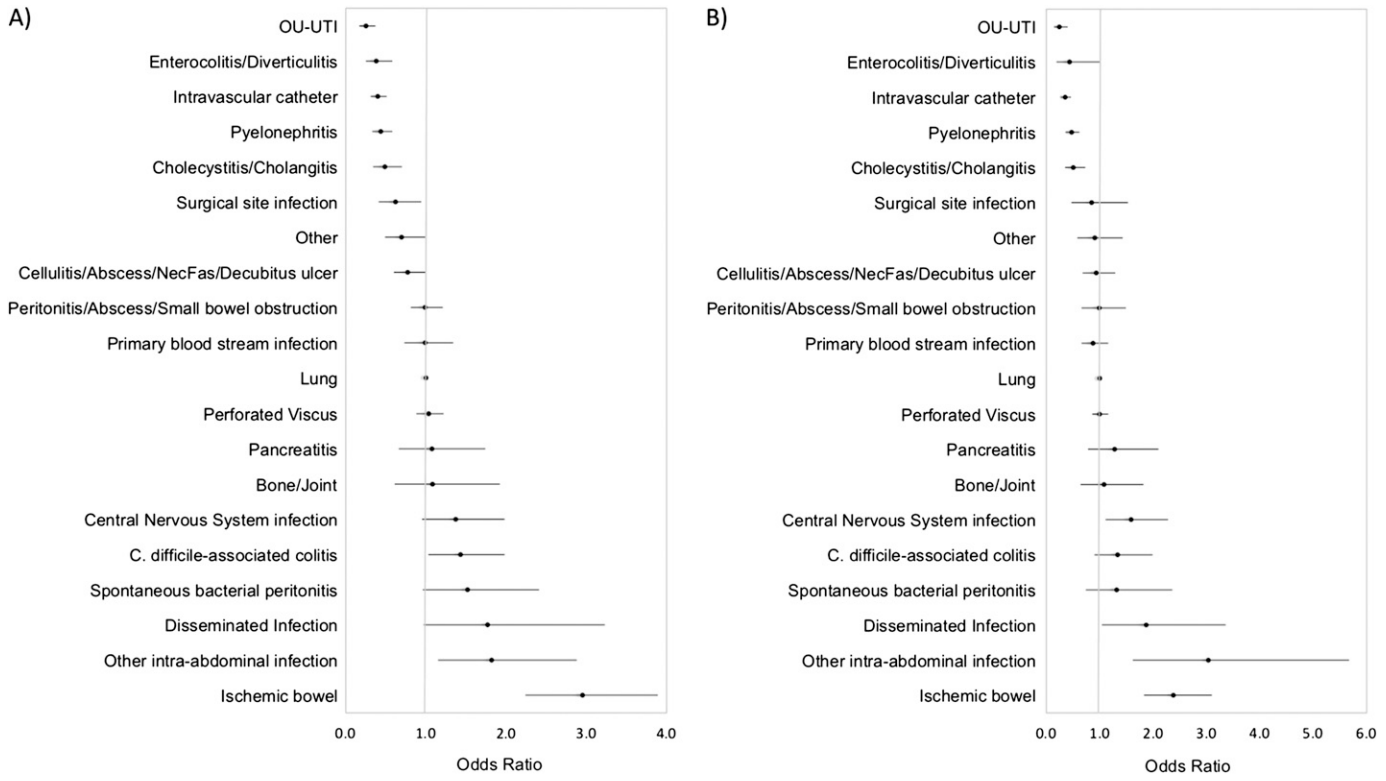

Figure 1. Relationship between source of infection and hospital mortality. Generalized estimating equations analysis was used to determine the odds ratio for hospital mortality, with lung as the reference anatomic source of infection. Data are reported as odds ratios ± 95% confidence intervals for adjusted hospital mortalities, presented from lowest to highest. Data were adjusted for (*A*) seven predisposing factors and (*B*) both seven predisposing and five downstream factors, outlined in Table 1. C. difficile = *Clostridium difficile*; NecFas = necrotizing fasciitis; OU-UTI = obstructive uropathy–associated urinary tract infection.

onset of hypotension to initiation of appropriate antimicrobials (Figure 3B), increased the amount of explained variation in risk of death by a minimal amount. Similar to predicted risk of death based on the logistic regression models, predicted risk of death at 28 days showed variation across anatomic sources, and some of this variation was modulated by adjustment for predisposing and downstream factors (Figure 4).

Sensitivity Analyses: Stratification by Category of Culture Results

Microbiologic characteristics of infection contribute to outcome of septic shock (27). To determine whether the association between the anatomic source of infection and hospital mortality varies according to the type of organism cultured, logistic regression analysis adjusted for predisposing factors, and predisposing plus downstream factors were applied separately to five groups according to category of culture results: gram-positive bacteria, gram-negative bacteria, culture-negative, *S. aureus*, and *E. coli* (*see* Figures E1A and E1B in the online supplement). Despite this stratification, there was still variation in hospital mortality across anatomic sources of infection and the anatomic sources of infection associated with the lowest and highest mortalities did not change. In the subgroup of patients who did not receive antimicrobial agents before the onset of hypotension, there was also variation in time to death in hospital across anatomic sources of infection (*see* Figures E2A and E2B).

Discussion

This study shows that anatomic source of infection is associated with hospital mortality in patients who have septic shock, and that variation in mortality by source of infection is independent of predisposing factors. Hospital mortality is highest for patients who have intraabdominal infection secondary to ischemic bowel and disseminated infections and lowest for those who have obstructive uropathy–associated urinary tract infection. Adjustment for some downstream factors does not explain residual variation after adjustment for predisposing factors. This suggests that even if interventions directly targeting these factors reduced mortality, heterogeneity in mortality across anatomic sources of infection would remain.

This study is the largest to date to evaluate the relationship between the anatomic source of infection and hospital mortality; our data span a nearly 20-year time period. The analysis included a comprehensive adjustment for multiple variables that are known to affect hospital mortality but that were not considered in previous studies of septic shock (16, 18, 19). In addition, to address secular trends, we adjusted for the year of admission for septic shock. Related studies have examined the role of anatomic source in outcomes from severe sepsis (28–30) and have found that urosepsis has a more favorable prognosis, whereas abdominal sources have a worse prognosis. However, none of these studies

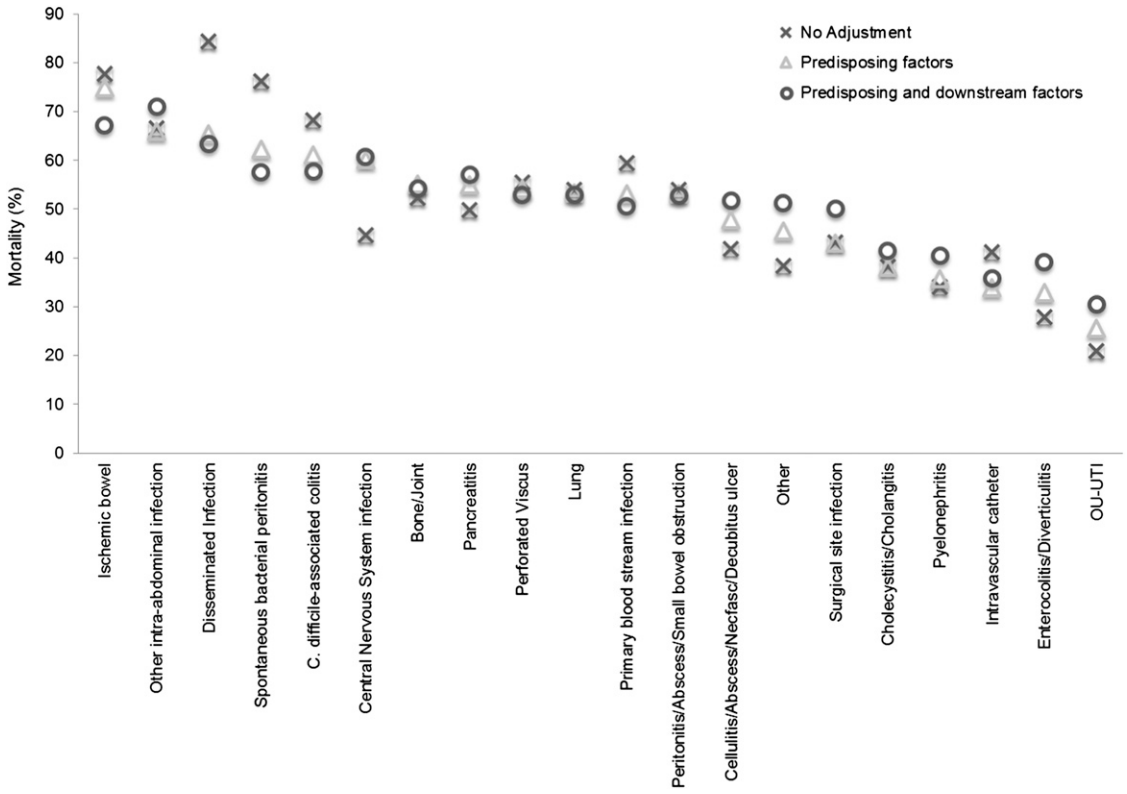

Figure 2. Comparison of unadjusted and adjusted standardized hospital mortality by anatomic source of infection. Hospital mortality unadjusted (*exes*), standardized hospital mortality adjusted for predisposing factors (*triangles*), and standardized hospital mortality adjusted for predisposing and downstream factors (*circles*) shown as percentage values, ordered from highest to lowest after adjusting for only predisposing factors. Adjustment influences the absolute difference and order of predicted mortality by anatomic site of infection. C. difficile = *Clostridium difficile*; NecFas = necrotizing fasciitis; OU-UTI = obstructive uropathy–associated urinary tract infection.

has included the sequential and detailed adjustment for predisposing and downstream factors that was done in the current analysis.

Over the nearly two decades during which our data were collected, management of septic shock has been transformed by landmark trials that highlight the importance of early, goal-directed resuscitation and antimicrobial therapy (3, 4). Over the last 10 years since the introduction of guidelines for management of severe sepsis and septic shock, there has been a decrease in hospital mortality for septic shock (11, 15). At the same time, several clinical trials of treatment for septic shock have not shown any differences between intervention and control groups (31–36). It is possible that this problem is caused by heterogeneity of patients enrolled in these trials. Given the important role of heterogeneity of treatment effect (37), understanding the role of anatomic source of infection may be useful in the design of future trials in more homogeneous groups of patients.

Severe sepsis and septic shock are driven by a profound proinflammatory state that initially contributes to eradication of invading pathogens but can eventually lead to an immunocompromised state and tissue destruction (36, 38–40). Our data suggest that the anatomic source of infection influences the outcome of septic shock independent of both predisposing and downstream physiologic and metabolic factors that may modulate the septic inflammatory response. It is notable that the poorest outcomes are associated with infections that have large burdens of organisms (ischemic bowel, disseminated infection). This large burden of organisms and antigens could contribute to systemic immune exhaustion, and potentially to irreversible immunosuppression, irrespective of predisposing factors and management strategies (39, 41).

In contrast, obstructive uropathy–associated urinary tract infection, an infection associated with lower risk of hospital mortality, may be an example of an anatomically protected site. The anatomic structure of the bladder and the genitourinary tract as well as the washout by micturition (42) may prevent bacterial invasion and limit absorption of microbes and bacterial toxins. Additionally, timely recognition of the source of infection and rapid source control by relieving obstruction may also contribute to the lower mortality noted for this anatomic source of infection.

An understanding of the role of anatomic source of infection in determining the mortality of septic shock may be useful for several reasons. The primary use may be in improving prognostication in septic shock (including revisions to prognostic scoring systems). Improved prognostication and identification of patients who are at higher risk of hospital mortality may help to select a patient population that could benefit from novel agents for management of septic shock. This kind of prognostication may also identify hospital patients who would benefit from intensive care monitoring.

Preserving host immune function may be an important advance in the

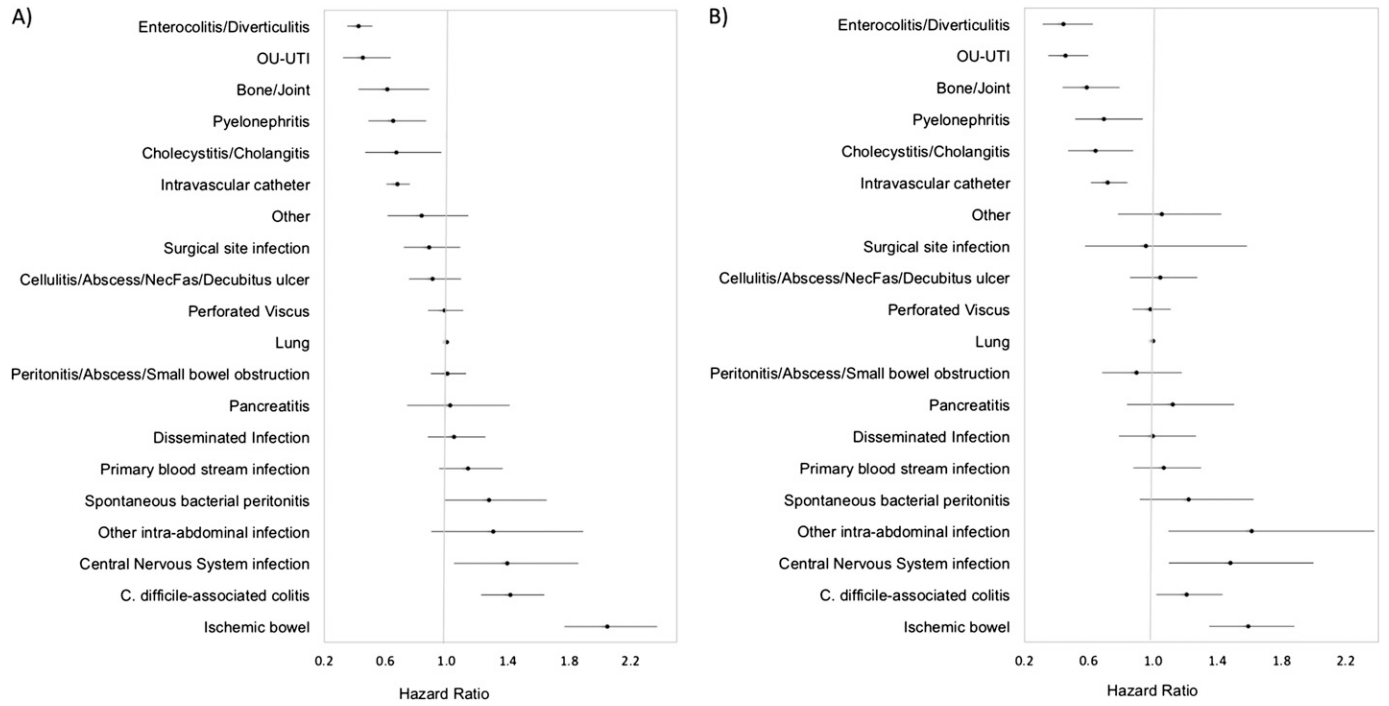

Figure 3. Relationship between anatomic source of infection and time to hospital death adjusted for predisposing factors (*A*), and predisposing and downstream factors including time to initiating appropriate antimicrobial therapy (*B*). Cox regression analysis was done on a subset of patients in whom antimicrobial agents were initiated after the onset of hypotension (n = 5,782). C. difficile = *Clostridium difficile*; NecFas = necrotizing fasciitis; OU-UTI = obstructive uropathy–associated urinary tract infection.

management of severe sepsis and septic shock (43). However, immunomodulatory agents have failed to improve outcome in these patients (44–47). It has been argued that failed phase III clinical trials that tested inhibitors of inflammation (44–47) have been inconclusive because of enrolment of subjects who had low and intermediate risk of death (48). Patients who have septic shock caused by more lethal infections, such as ischemic bowel and disseminated infection, may be better candidates for trials of these kinds of agents.

Although administration of early empiric broad-spectrum antimicrobial therapy is foundational to the successful management of septic shock (4, 20, 49–52), deescalation from broad to narrower-spectrum antimicrobial therapy is also important because overuse of antimicrobial agents can lead to avoidable adverse drug events and antimicrobial resistance. However, uncertainty remains about when deescalation is safe in patients who have severe sepsis or septic shock (53–55); this topic warrants randomized controlled trials (55). The finding that patients who have septic shock caused by obstructive uropathy–associated urinary tract infection and certain other infections are at lower risk of hospital mortality may identify a patient population that may be safely included in studies of these strategies.

The persistent variation in hospital mortality by anatomic source of infection among patients whose infections are associated with gram-positive bacteria, gram-negative bacteria, no positive culture, *S. aureus*, or *E. coli* suggests that the effect of anatomic source of infection on outcome is independent of the type of causative organism. The impact of microbiologic characteristics may be masked once severe sepsis and associated organ failure set in (19).

There are several limitations of this study. First, although we adjusted for several predisposing patient factors that might explain the variation in hospital mortality across sources of infection, there may be other confounding factors or effect modifiers that we did not measure. For example, we did not have any information about resuscitation practices. Second, because this study was predominantly conducted in Canadian and American centers, our results might not be extrapolated to a non–North American setting. Third, we considered only hospital mortality and not longer-term outcomes (except in the predicted standardized mortality analysis). Finally, the results of the analyses adjusting for downstream factors should be viewed as tentative because of nonidentifiability of direct effects in regression models with mediators.

Strengths of this study include the large population, multiple centers in several countries, and the sequential approach to adjustment and time-dependent outcomes in our analysis.

Conclusions

Anatomic source of infection is associated with hospital mortality in crude analysis and after adjustment for predisposing factors (year of septic shock diagnosis, patient age and sex, source of admission, baseline comorbidities, community- vs. hospital-acquired infection, and organism type) and downstream factors (APACHE-II score, number of Day 1 organ failures, bacteremia, timing and appropriateness of antimicrobial agents, and adjunct therapy). Therefore, anatomic source of infection should be

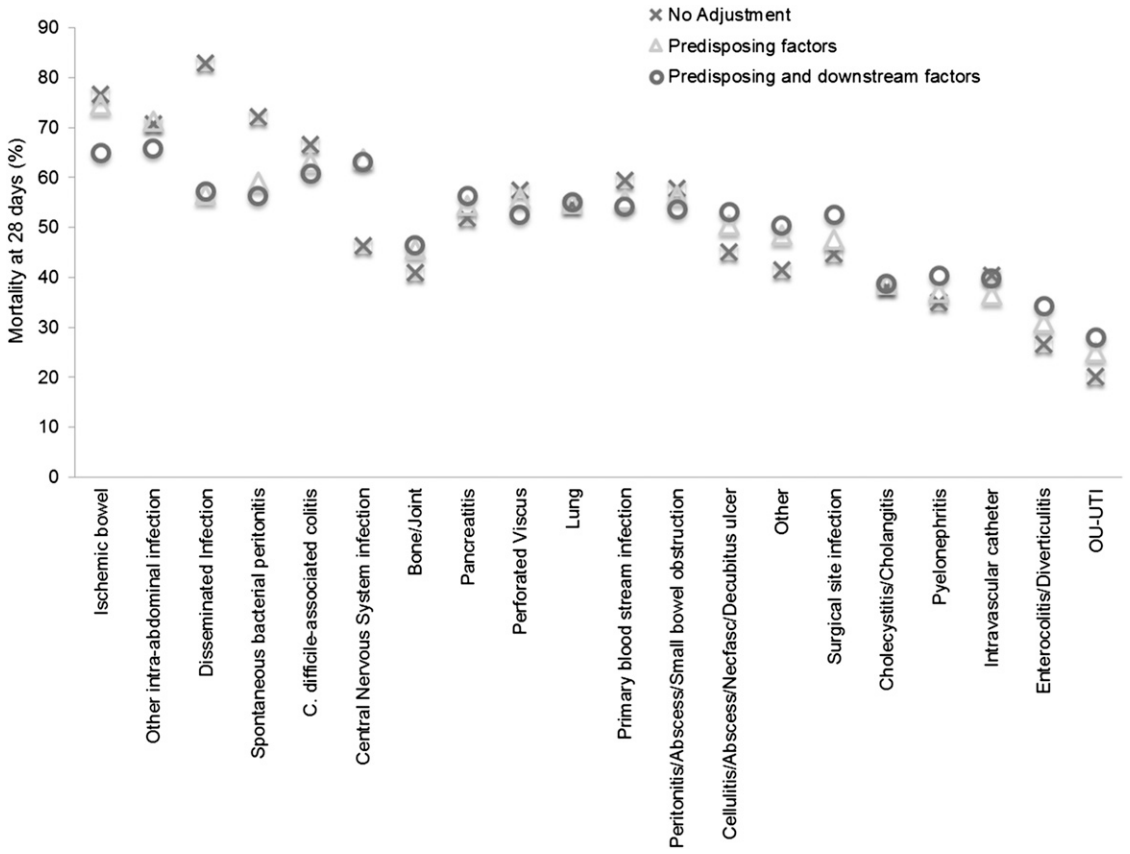

Figure 4. Comparison of unadjusted and adjusted standardized mortality at 28-day follow-up by anatomic source of infection. Hospital mortality unadjusted (*exes*), standardized hospital mortality adjusted for predisposing factors (*triangles*), and standardized hospital mortality adjusted for predisposing and downstream factors (*circles*) shown as percentage values, ordered from highest to lowest after adjusting for only predisposing factors. Adjustment influences the absolute difference and order of predicted mortality by anatomic site of infection. C. difficile = *Clostridium difficile*; NecFas = necrotizing fasciitis; OU-UTI = obstructive uropathy–associated urinary tract infection.

considered in future trial designs and data analyses, and in development of new prognostic scoring systems for patients who have septic shock. ■

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