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ORIGINAL RESEARCH

The Epidemiology of Acute Organ System Dysfunction From Severe Sepsis Outside of the Intensive Care Unit

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BACKGROUND: Severe sepsis is a common, costly, and complex problem, the epidemiology of which has only been well studied in the intensive care unit (ICU). However, nearly half of all patients with severe sepsis are cared for outside the ICU.

OBJECTIVE: To determine rates of infection and organ system dysfunction in patients with severe sepsis admitted to non-ICU services.

DESIGN: Retrospective cohort study.

SETTING: A large, tertiary, academic medical center in the United States.

PATIENTS: Adult patients initially admitted to non-ICU medical services from 2009 through 2010.

MEASUREMENTS: All International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes were screened for severe sepsis. Three hospitalists reviewed a sample of medical records evaluating the characteristics of severe sepsis.

RESULTS: Of 23,288 hospitalizations, 14% screened positive for severe sepsis. A sample of 111 cases was manually reviewed, identifying 64 cases of severe sepsis. The mean age of patients with severe sepsis was 63 years, and 39% were immunosuppressed prior to presentation. The most common site of infection was the urinary tract (41%). The most common organ system dysfunctions were cardiovascular (hypotension) and renal dysfunction occurring in 66% and 64% of patients, respectively. An increase in the number of organ systems affected was associated with an increase in mortality and eventual ICU utilization. Severe sepsis was documented by the treating clinicians in 47% of cases.

CONCLUSIONS: Severe sepsis was commonly found and poorly documented on the wards at our medical center. The epidemiology and organ dysfunctions among patients with severe sepsis appear to be different from previously described ICU severe sepsis populations. *Journal of Hospital Medicine* 2013;8:243–247. © 2013 Society of Hospital Medicine

The International Consensus Conference (ICC) for sepsis defines severe sepsis as an infection leading to acute organ dysfunction.[1,2] Severe sepsis afflicts over 1 million patients each year in Medicare alone, and is substantially more common among older Americans than acute myocardial infarction.[3–5] Recently, the Agency for Healthcare Research and Quality identified severe sepsis as the single most expensive cause of hospitalization in the United States.[6] The incidence of severe sepsis continues to rise.[4,5]

Severe sepsis is often mischaracterized as a diagnosis cared for primarily in the intensive care unit (ICU). Yet, studies indicate that only 32% to 50% of patients with severe sepsis require ICU care, leaving the majority on the general care wards.[7,8] These studies also reveal mortality rates of 26% to 30% among patients with severe sepsis who are not admitted to an ICU compared to 11% to 33% in the ICU.[7,8]

Although a number of epidemiologic and interventional studies have focused on severe sepsis in the ICU,[3,9,10] much less is known about patients cared for on the general medicine wards. Without this information, clinicians cannot make informed choices about important management decisions such as targeted diagnostic testing, empirical antimicrobials, and other therapies. To this end, we sought to further characterize the infectious etiologies and resultant organ system dysfunctions in the subset of patients with severe sepsis admitted to non-ICU medical services at a tertiary academic medical center.

METHODS

Population/Setting

All hospitalizations of adult patients (≥18 years old) who were initially admitted to non-ICU medical services at the University of Michigan Hospital during 2009 through 2010 were included. The University of Michigan Hospital has 610 general medical-surgical beds, including telemetry beds, with closed ICUs

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comprised of 179 beds staffed by intensivists. Patients transferred from other hospitals and those admitted to non-medical services were excluded.

Data Abstraction and Definitions

All International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes for hospitalizations were screened using a previously published and validated algorithm for severe sepsis.[11] Following this screening, 3 randomly selected round-numbered batches of hospitalizations were sampled with subsequent application of the exclusion criteria. Medical records including physicians' notes, consultants' notes, nurses' notes, physical therapy notes, discharge coordinators' notes, emergency room flow sheets, as well as ward flow sheets were reviewed in detail by 3 practicing hospitalists using a structured instrument closely aligned with the ICC definition of severe sepsis.[2] We also sampled a smaller number of patients whose ICD-9-CM diagnoses screened negative for severe sepsis. Sample size was selected as part of a project with multiple objectives, and reflected a pragmatic balance between the anticipated precision of the results and the resources available to conduct chart review.[11] All discrepancies were reconciled among the 3 reviewers.

Reviewers first assessed whether infection was present, then evaluated for evidence of each organ system dysfunction, and finally determined the extent to which those organ dysfunctions were a response to the infection. Infection was defined either as a patient with a microbiologic culture growing a pathologic organism in a normally sterile site or documentation of a suspected infection with other confirmatory evidence (radiological, physical exam finding) with resultant systemic inflammatory response and administration of antimicrobials. Community-acquired and healthcare-associated infections were not differentiated. Microbiologic data, confirmatory tests, and site of infection were abstracted in detail.

Organ dysfunction was defined as per the 2001 ICC criteria,[2] and was assessed for neurological, pulmonary, cardiovascular, renal, gastrointestinal, hematological, and hepatic system involvement in all patients. A summary of these clinical definitions is included in Table 1. Data on important comorbidities were also abstracted. Immunosuppression was defined as having any of the following: solid organ transplant, bone marrow/stem cell transplant, human immunodeficiency virus/acquired immunodeficiency syndrome, neutropenia (absolute neutrophil count <1000), hematologic malignancy, solid organ malignancy with chemotherapy within the past 12 months, or pharmacologic immunosuppression (prednisone >20 mg daily for >4 weeks, calcineurin inhibitor, methotrexate, tumor necrosis factor inhibitors, azathioprine, sulfasalazine, hydroxychloroquine). Last, each chart was evaluated for the presence of explicit documentation with the presence of the words or phrases: "sepsis," "septic shock," or "severe sepsis," indicating that the clinical service recognized and fully documented that a patient had severe sepsis.

TABLE 1. Organ System Dysfunction Parameters as Defined by the 2001 International Consensus Conference[1,2]

Organ System	Parameters to Indicate Dysfunction
Cardiovascular	Systolic BP <90, elevated lactate, MAP <70, requiring pressors >2 hours, decrease in systolic BP of >40
Renal	Creatinine increase >0.5 mg/dL, oliguria
Neurological	Acute mental status changes
Pulmonary	Intubation, BiPAP, supplemental oxygen >6 LPM or 40% face mask, PaO2/FiO2 <300
Hematologic	INR >1.5 or PTT >60 not on anticoagulation, platelets <100 or 50% of baseline
Ileus	Decreased bowel motility requiring a change in diet
Hepatic	Bilirubin >4 mg/dL and >1.5 × baseline

NOTE: Abbreviations: BiPAP, bilevel positive airway pressure, BP, blood pressure; dL, deciliter; FiO2, fraction of inspired oxygen; INR, international normalized ratio; LPM, liters per minute; MAP, mean arterial pressure; mg, milligram; PaO2, partial pressure of oxygen in arterial blood; PTT, partial thromboplastin time.

Data Analysis

Methods for assessment of reviewer concordance have been previously described and were summarized using the kappa statistic.[11] Initial data extraction was performed in SAS 9.1 (SAS Institute, Cary, NC) and all analyses were conducted in Stata 12 (StataCorp LP, College Station, TX). Binomial 95% confidence intervals (CIs) are presented. This project was approved by the University of Michigan Institutional Review Board.

RESULTS

Of 23,288 hospitalizations examined from 2009 through 2010, the ICD-9–based automated screen for severe sepsis was positive for 3,146 (14 %). A random sample of 111 medical records, of which 92 had screened positive for severe sepsis and 19 had screened negative, was reviewed in detail. After review by the hospitalists, 64 of these 111 hospitalizations were judged to have severe sepsis, 61 of the 92 screened positive cases (66%), and 3 of the 19 screened negative cases (16%). The 3 reviewers had a kappa of 0.70, indicating good agreement.

Characteristics of the 64 patients with severe sepsis are shown in Table 2. The mean age was 63 years old (standard deviation [SD]=17.7), and 41% were male. The mean length of stay was 13.7 days (SD=20.8). Thirty-nine percent (95% CI, 27%-52%) of patients (25/64) were immunosuppressed. Of patients initially admitted to the general medical ward, 25% (16/64; 95% CI, 15%-37%) ultimately required ICU care during their admission. The overall in-hospital mortality rate was 13% (8/64; 95% CI, 6%-23%). Immunosuppressed patients had a mortality rate of 20% and non-immunosuppressed patients had a mortality rate of 8%. Only 47% (30/64; 95% CI, 34%-60%) of the

TABLE 2. Demographics and Characteristics of Patients With Severe Sepsis (N=64)

Age, mean (SD), y	63 (18)
Male sex, no. (%)	26 (41)
Preexisting conditions, no. (%)	
History of diabetes	20 (31)
End stage renal disease on chronic dialysis	2 (3)
Chronic obstructive pulmonary disease on oxygen	3 (5)
History of cancer	15 (23)
Liver cirrhosis	5 (8)
Immunosuppression	25 (39)
Median length of stay (days)	7.5
Mean length of stay (SD)	13.7 (20.8)

NOTE: **Abbreviations**: SD, standard deviation.

medical records had explicit clinician documentation of severe sepsis.

The most common site of infection was found to be the genitourinary system, occurring in 41% (26/64; 95% CI, 29%-54%) of patients (Table 3). Pulmonary and intra-abdominal sites were also common, accounting for 14% (95% CI, 6.6%-25%) and 13% (95% CI, 5.6%-23%) of sites, respectively. An infecting organism was identified by culture in 66% (42/64; 95% CI, 53%-77%) of case patients with specific pathogens listed in Table 4. Among patients with positive culture results, the majority grew Gram-negative organisms (57%; 95% CI, 41%-72%). Non-*Clostridium difficile* Gram-positive organisms were also prominent and identified in 48% (95% CI, 32%-64%) of positive cultures. *Candida* was less common (12%, 95% CI, 4.0%-26%). Fourteen cases (22%, 95% CI, 10%-30%) had 2 or more concomitant infectious pathogens.

All 64 patients had at least 1 organ dysfunction, as required by the ICC definition of severe sepsis. Organ dysfunction in 2 or more organ systems occurred in 77% (95% CI, 64%-86%) of the cases (49/64). The incidence for each organ system dysfunction is presented in Table 5, as well as its relationship to both mortality and ICU admission. The most common organ system dysfunctions were found to be cardiovascular (hypotension) and renal dysfunction occurring in 66% and 64% of the cases, respectively.

TABLE 3. Site of Infection (N=64)

Site	No. (%)
Genitourinary	26 (41)
Pulmonary	9 (14)
Intra-abdominal (not intraluminal)	8 (13)
Bloodstream/cardiac	5 (8)
Skin and soft tissue	4 (6)
GI lumen	4 (6)
Joint	2 (3)
Multiple sites	4 (6)
Unknown	2 (2)

NOTE: **Abbreviations**: GI, gastrointestinal.

TABLE 4. Microbiology

	Absolute Frequency, Total Positive Culture Results, N=64, No. (%)*	Patients With Cultures Growing at Least One of the Pathogens, N=42, No. (%)*
Gram-negative pathogens	30 (47)	24 (57)
Escherichia coli	12 (19)	12 (29)
Escherichia coli (multidrug resistant)	2 (3)	2 (5)
Klebsiella	6 (9)	5 (12)
Pseudomonas aeruginosa	6 (9)	4 (10)
Pseudomonas aeruginosa (multidrug resistant)	2 (3)	2 (5)
Other†	6 (9)	6 (14)
Gram-positive pathogens	29 (45)	25 (59)
Enterococcus	14 (22)	13 (31)
Vancomycin-resistant *Enterococcus* species	5 (8)	4 (10)
Staphylococcus aureus	7 (11)	7 (17)
Methicillin-resistant *Staphylococcus aureus*	3 (5)	3 (7)
Streptococcus pneumoniae	2 (3)	2 (5)
Coagulase-negative *staphylococci*	1 (2)	1 (2)
Clostridium difficile	5 (8)	5 (12)
Fungi		
Candida species	5 (8)	5 (12)
Mycobacterium avium	1 (2)	1 (2)
Two organisms		9 (21)
Three or more organisms		5 (12)

*Multiple responses per patient possible. †Other includes *Citrobacter, Enterobacter, Proteus, Achromobacter xylosoxidans,* and *Fusobacterium*.

In this non-ICU population, pulmonary dysfunction occurred in 30% of cases, but was frequently associated with transfer to the ICU, as 63% of the patients with pulmonary failure required ICU care. Patients with more organ systems affected were more likely to be transferred to the ICU and to die.

TABLE 5. Incidence and Outcomes of Organ Dysfunction in Patients Admitted to Non-ICU Services

	No. (%)	ICU Transfer, No. (%)	Mortality, No. (%)
Number of failed organs, N = 64			
1	15 (23%)	0 (0%)	0 (0%)
2	25 (39%)	2 (8%)	0 (0%)
3	7 (11%)	2 (29%)	1 (14%)
4	10 (16%)	6 (60%)	3 (30%)
>4	7 (11%)	6 (86%)	4 (57%)
Types of organ system dysfunction, all patients, N = 64*			
Cardiovascular	42 (66%)	16 (38%)†	8 (19%)‡
Renal	41 (64%)	10 (24%)†	5 (12%)‡
Central nervous system	35 (54%)	14 (40%)†	7 (18%)‡
Pulmonary	19 (30%)	12 (63%)†	8 (42%)‡
Hematologic	15 (23%)	6 (40%)†	6 (40%)‡
GI (ileus)	8 (13%)	5 (63%)†	1 (13%)‡
Hepatic	5 (8%)	4 (80%)†	2 (40%)‡

NOTE: **Abbreviations**: GI, gastrointestinal; ICU, intensive care unit.

*Multiple responses per patient possible. †Percentage of patients with each organ system dysfunction who needed ICU care while in the hospital. ‡Percentage of patients with organ system dysfunction who died while in the hospital.

DISCUSSION

Severe sepsis was common among patients admitted to the general medical ward in this tertiary care center. Our patient cohort differed in important ways from previously described typical cases of severe sepsis among ICU populations. Severe sepsis on the general medical wards was more commonly associated with Gram-negative pathogens in the setting of genitourinary tract infections. This is in contrast to Gram-positive organisms and respiratory tract infections, which are more common in the ICU.[3,10] Renal and cardiac dysfunction were commonly observed organ failures, whereas in the ICU, severe sepsis has been reported to more likely involve respiratory failure. These results suggest that hospitalists seeking to provide evidence-based care to prevent postsepsis morbidity and mortality for their non-ICU patients need to heighten their index of suspicion when caring for an infected patient and appreciate that many severe sepsis patients may not fit neatly into traditional sepsis treatment algorithms.

Studies characterizing severe sepsis in the ICU setting indicate a predominance of pulmonary infections and respiratory failure with occurrence rates of 74% to 95% and 54% to 61%, respectively.[3,12,13] Given that either shock or pulmonary dysfunction is often required for admission to many ICUs, it is perhaps not surprising that these rates are dramatically different on the general medicine ward, with a relative scarcity of pulmonary infections (14%) and respiratory dysfunction (30%). Instead, genitourinary infections were noted in 41% (95% CI, 29%-54%) of the cases, in contrast to the rates of genitourinary infections in ICU patients with severe sepsis, which have rates of 5.4% to 9.1%.[3,10] Likely as a result of this, a Gram-negative predominance is noted in the associated microbiology. Furthermore, our study indicates that *C difficile* and vancomycin-resistant *Enterococcus* (VRE) species appear to represent an emerging cause of severe sepsis on the general medicine wards, as they have not been noted to be causative microorganisms in previous studies of sepsis. This is concordant with other studies showing increases in incidence and severity of disease for *C difficile* as well as VRE.[14,15]

Previous epidemiologic studies of severe sepsis originating outside the ICU are lacking, but some work has been done. One study on the epidemiology of sepsis both with and without organ dysfunction aggregated all hospitalized patients and included those both admitted to the general medicine wards and directly to the ICU.[7] Similar to our study, this study also found a predominance of Gram-negative causative organisms, as well as comparable in-hospital mortality rates (12.8% vs 13%). Additionally, genitourinary infections were noted in 20% of the patients, notably higher than rates reported to have been found in patients with severe sepsis in the ICU, but not the magnitude found in our study, perhaps as a result of the combined ICU-ward population studied. A similar high prevalence of genitourinary infections was also noted in a recent administrative data-based study of emergency medical services-transported patients with severe sepsis, half of whom required intensive care during their hospitalization.[16]

Our study is unique in that it focuses on severe sepsis in patients, commonly cared for by hospitalists, who were admitted to the general medical ward, and uses patient level data to elucidate more characteristics of the defining organ dysfunction. Furthermore, our results suggest that severe sepsis was poorly documented in this setting, indicating a potential impact on billing, coding, case mix index, and hospital mortality statistics that rely on very specific wording, as well as a possible need for increased awareness among hospitalists. Without this awareness, an opportunity may be missed for improved patient care via specific sepsis-targeted measures,[13,17,18] including more aggressive resuscitative measures[19] or intensive physical and occupational therapy interventions aimed at impacting the cognitive and functional debilities[20] that result from severe sepsis. Highlighting this growing need to better assist clinicians assess the severity of septic patients and recognize these complex cases on the general medicine wards, 1 recent study evaluated the fitness of several clinical disease-severity scoring systems for patients with sepsis in general internal medicine departments.[21] Perhaps with the help of tools such as these, which are being piloted in some hospitals, the care of this growing population can be enhanced.

Our study has a number of limitations that should be kept in mind. First, this is a single center study performed at an academic tertiary care center with a relatively high incidence of immunosuppression, which may influence the spectrum of infecting organisms. Our center also has a relatively large, closed-model ICU, which often operates at near capacity, potentially affecting the severity of our non-ICU population. Second, although we screened a large number of patients, as necessitated by our intensive and detailed review of clinical information, our sample size with hospitalist-validated severe sepsis is relatively small. With this small sample size, less prevalent infections, patient characteristics, and organ dysfunctions may by chance have been under or over-represented, and one could expect some variance in the occurrence rates of organ system dysfunction and infection rates by sampling error alone. Further larger scale studies are warranted to confirm these data and their generalizability. Third, the data necessary to calculate sequential organ failure assessment or multiple organ dysfunction score were not collected. This may limit the ability to directly compare the organ dysfunction noted in this study with others. Additionally, given the ICC definitions of organ dysfunction, some of the

organ dysfunction noted, particularly for neurological dysfunction, was reliant on subjective clinical findings documented in the record. Finally, we relied on the lack of specific terminology to indicate a lack of documentation of sepsis, which does not necessarily indicate a lack of recognition or undertreatment of this condition. However, these limitations are offset by the strengths of this study, including the patient-level medical record validation of severe sepsis by trained hospitalist physicians, high kappa statistic, and strict application of guideline-based definitions.

This work has important implications for both clinicians and for future research on severe sepsis. The results suggest that severe sepsis may be quite common outside the ICU, and that patients presenting with this condition who are admitted to general medical wards are not routinely characterized by the profound hypoxemia and refractory shock of iconic cases. Certainly, further study looking at larger numbers of cases is needed to better understand the specifics and nuances of this important topic as well as to further evaluate clinicians' ability to recognize and treat such patients in this setting. Furthermore, future research on the treatment of severe sepsis, including both antimicrobials and disease-modifying agents (eg, anti-inflammatories) must continue to include and even focus on this large population of non-ICU patients with severe sepsis, as the risk/benefit ratios of such potential treatments may vary with severity of illness.

In conclusion, severe sepsis was commonly found in patients admitted on the general medicine wards. The epidemiology of the infections and resultant organ dysfunction appears to differ from that found in the ICU. More studies are needed to provide a deeper understanding of this disease process, as this will enable clinicians to better recognize and treat patients thus afflicted, no matter the setting.

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