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ORIGINAL RESEARCH

Risk Factors for 30-Day Readmission Among Patients With Culture-Positive Severe Sepsis and Septic Shock: A Retrospective Cohort Study

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BACKGROUND: With decreasing mortality in sepsis, attention has shifted to longer-term consequences associated with survivorship. Thirty-day readmission as a component of healthcare utilization is an important outcome.

OBJECTIVE: To examine the frequency of and risk factors for 30-day readmission among patients surviving sepsis.

DESIGN: Single-center retrospective cohort.

METHODS/SETTING: We examined 30-day readmission risk among survivors of hospitalization with culture-positive severe sepsis or septic shock. Extended spectrum β-lactamase (ESBL) organisms were identified via molecular laboratory testing. Healthcare-associated (HCA) was defined by 1 of the following: (1) recent hospitalization, (2) immune suppression, (3) nursing home residence, (4) hemodialysis, (5) prior antibiotics, and (6) index bacteremia hospital-acquired (onset >2 days following admission). Acute kidney injury (AKI) was defined according to the RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria. Logistic regression modeled predictors of 30-day readmission.

RESULTS: Among 1697 sepsis survivors, 543 (32.0%) required 30-day readmission. Readmitted patients had a higher chronic (median Charlson score 5 vs 4, $P < 0.001$) but not acute (median APACHE [Acute Physiology and Chronic Health Evaluation] II score 15 and 15, $P = 0.275$) illness burden, and higher prevalence of HCA sepsis (94.2% vs 90.2%, $P = 0.014$) than nonreadmitted survivors. In logistic regression, 3 factors increased (Organism: ESBL [odds ratio {OR}: 4.50, 95% confidence interval {CI}: 1.43–14.19], RIFLE: Injury or RIFLE: Failure [OR: 1.95, 95% CI: 1.300–2.93], and Organism: *Bacteroides* spp [OR: 2.04, 95% CI: 1.06–3.95]) and 2 reduced (Source: Urine [OR: 0.58, 95% CI: 0.35–0.98], Organism: *Escherichia coli* [OR: 0.49, 95% CI: 0.27–0.90]) the odds of 30-day readmission.

CONCLUSIONS: One-third of survivors of severe sepsis/septic shock required 30-day readmission. Mild-to-moderate AKI nearly doubled its risk. *Journal of Hospital Medicine* 2015;10:678–685. © 2015 Society of Hospital Medicine

Despite its decreasing mortality, sepsis remains a leading reason for intensive care unit (ICU) admission and is associated with crude mortality in excess of 25%.[1,2] In the United States there are between 660,000 and 750,000 sepsis hospitalizations annually, with the direct costs surpassing $24 billion.[3–5] As mortality rates have begun to fall, attention has shifted to issues of morbidity and recovery, the intermediate and longer-term consequences associated with survivorship, and how interventions made while the patient is acutely ill in the ICU alter later health outcomes.[3,5–8]

One area of particular interest is the need for healthcare utilization following an acute admission for sepsis, and specifically rehospitalization within 30 days of discharge. This outcome is important not just from the perspective of the patient's well-being, but also from the point of view of healthcare financing. Through the establishment of Hospital Readmission Reduction Program, the Centers for Medicare and Medicaid Services have sharply reduced reimbursement to hospitals for excessive rates of 30-day readmissions.[9]

For sepsis, little is known about such readmissions, and even less about how to prevent them. A handful of studies suggest that this rate is between 5% and 26%.[10–13] Whereas some of these studies looked at some of the factors that impact readmissions,[11,12] none examined the potential contribution of microbiology of sepsis to this outcome.

To explore these questions, we conducted a single-center retrospective cohort study among critically ill patients admitted to the ICU with severe culture-positive sepsis and/or septic shock and determined the rate of early post–hospital discharge readmission. In addition, we sought to elucidate predictors of subsequent readmission.

METHODS

Study Design and Ethical Standards

We conducted a single-center retrospective cohort study from January 2008 to December 2012. The

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study was approved by the Washington University School of Medicine Human Studies Committee, and informed consent was waived because the data collection was retrospective without any patient-identifying information. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Aspects of our methodology have been previously published.[14]

Primary Endpoint

All-cause readmission to an acute-care facility in the 30 days following discharge after the index hospitalization with sepsis served as the primary endpoint. The index hospitalizations occurred at the Barnes-Jewish Hospital, a ~1200-bed inner-city academic institution that serves as the main teaching institution for BJC HealthCare, a large integrated healthcare system of both inpatient and outpatient care. BJC includes a total of 13 hospitals in a compact geographic region surrounding and including St. Louis, Missouri, and we included readmission to any of these hospitals in our analysis. Persons treated within this healthcare system are, in nearly all cases, readmitted to 1 of the system's participating 13 hospitals. If a patient who receives healthcare in the system presents to an out-of-system hospital, he/she is often transferred back into the integrated system because of issues of insurance coverage.

Study Cohort

All consecutive adult ICU patients were included if (1) They had a positive blood culture for a pathogen (Cultures positive only for coagulase negative *Staphylococcus aureus* were excluded as contaminants.), (2) there was an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code corresponding to an acute organ dysfunction,[4] and (3) they survived their index hospitalization. Only the first episode of sepsis was included as the index hospitalization.

Definitions

All-cause 30-day readmission, was defined as a repeat hospitalization within 30 days of discharge from the index hospitalization among survivors of culture-positive severe sepsis or septic shock. The definition of severe sepsis was based on discharge ICD-9-CM codes for acute organ dysfunction.[3] Patients were classified as having septic shock if vasopressors (norepinephrine, dopamine, epinephrine, phenylephrine, or vasopressin) were initiated within 24 hours of the blood culture collection date and time.

Initially appropriate antimicrobial treatment (IAAT) was deemed appropriate if the initially prescribed antibiotic regimen was active against the identified pathogen based on in vitro susceptibility testing and administered for at least 24 hours within 24 hours following blood culture collection. All other regimens were classified as non-IAAT. Combination antimicrobial treatment was not required for IAAT designation.[15] Prior antibiotic exposure and prior hospitalization occurred within the preceding 90 days, and prior bacteremia within 30 days of the index episode. Multidrug resistance (MDR) among Gram-negative bacteria was defined as nonsusceptibility to at least 1 antimicrobial agent from at least 3 different antimicrobial classes.[16] Both extended spectrum β-lactamase (ESBL) organisms and carbapenemase-producing Enterobacteriaceae were identified via molecular testing.

Healthcare-associated (HCA) infections were defined by the presence of at least 1 of the following: (1) recent hospitalization, (2) immune suppression (defined as any primary immune deficiency or acquired immune deficiency syndrome or exposure within 3 prior months to immunosuppressive treatments—chemotherapy, radiation therapy, or steroids), (3) nursing home residence, (4) hemodialysis, (5) prior antibiotics. and (6) index bacteremia deemed a hospital-acquired bloodstream infection (occurring >2 days following index admission date). Acute kidney injury (AKI) was defined according to the RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria based on the greatest change in serum creatinine (SCr).[17]

Data Elements

Patient-specific baseline characteristics and process of care variables were collected from the automated hospital medical record, microbiology database, and pharmacy database of Barnes-Jewish Hospital. Electronic inpatient and outpatient medical records available for all patients in the BJC HealthCare system were reviewed to determine prior antibiotic exposure. The baseline characteristics collected during the index hospitalization included demographics and comorbid conditions. The comorbidities were identified based on their corresponding ICD-9-CM codes. The Acute Physiology and Chronic Health Evaluation (APACHE) II and Charlson comorbidity scores were calculated based on clinical data present during the 24 hours after the positive blood cultures were obtained.[18] This was done to accommodate patients with community-acquired and healthcare-associated community-onset infections who only had clinical data available after blood cultures were drawn. Lowest and highest SCr levels were collected during the index hospitalization to determine each patient's AKI status.

Statistical Analyses

Continuous variables were reported as means with standard deviations and as medians with 25th and 75th percentiles. Differences between mean values were tested via the Student *t* test, and between medians using the Mann-Whitney *U* test. Categorical data were summarized as proportions, and the χ^2 test

TABLE 1. Baseline Characteristics of Patients and Sepsis-Related Parameters at Index Hospitalization

	30-Day Readmission = Yes		30-Day Readmission = No		
	N = 543	% = 32.00%	N = 1,154	% = 68.00%	*P* Value
Baseline characteristics					
Age, y					
Mean ± SD	58.5 ± 15.7		59.5 ± 15.8		
Median (25, 75)	60 (49, 69)		60 (50, 70)		0.297
Race					
Caucasian	335	61.69%	769	66.64%	0.046
African American	157	28.91%	305	26.43%	0.284
Other	9	1.66%	22	1.91%	0.721
Sex, female	244	44.94%	537	46.53%	0.538
Admission source					
Home	374	68.88%	726	62.91%	0.016
Nursing home, rehab, or LTAC	39	7.81%	104	9.01%	0.206
Transfer from another hospital	117	21.55%	297	25.74%	0.061
Comorbidities					
CHF	131	24.13%	227	19.67%	0.036
COPD	156	28.73%	253	21.92%	0.002
CLD	83	15.29%	144	12.48%	0.113
DM	175	32.23%	296	25.65%	0.005
CKD	137	25.23%	199	17.24%	<0.001
Malignancy	225	41.44%	395	34.23%	0.004
HIV	11	2.03%	10	0.87%	0.044
Charlson comorbidity score					
Mean ± SD	5.24 ± 3.32		4.48 ± 3.35		
Median (25, 75)	5 (3, 8)		4 (2, 7)		<0.001
HCA RF	503	94.19%	1,019	90.66%	0.014
Hemodialysis	65	12.01%	114	9.92%	0.192
Immune suppression	193	36.07%	352	31.21%	0.044
Prior hospitalization	339	65.07%	620	57.09%	0.002
Nursing home residence	39	7.81%	104	9.01%	0.206
Prior antibiotics	301	55.43%	568	49.22%	0.017
Hospital-acquired BSI*	240	44.20%	485	42.03%	0.399
Prior bacteremia within 30 days	88	16.21%	154	13.34%	0.116
Sepsis-related parameters					
LOS prior to bacteremia, d					
Mean ± SD	6.65 ± 11.22		5.88 ± 10.81		
Median (25, 75)	1 (0, 10)		0 (0, 8)		0.250
Surgery					
None	362	66.67%	836	72.44%	0.015
Abdominal	104	19.15%	167	14.47%	0.014
Extra-abdominal	73	13.44%	135	11.70%	0.306
Status unknown	4	0.74%	16	1.39%	0.247
Central line	333	64.41%	637	57.80%	0.011
TPN at the time of bacteremia or prior to it during index hospitalization	52	9.74%	74	5.45%	0.017
APACHE II					
Mean ± SD	15.08 ± 5.47		15.35 ± 5.43		
Median (25, 75)	15 (11, 18)		15 (12, 19)		0.275
Severe sepsis	361	66.48%	747	64.73%	0.480
Septic shock requiring vasopressors	182	33.52%	407	35.27%	
On MV	104	19.22%	251	21.90%	0.208
Peak WBC (103/μL)					
Mean ± SD	22.26 ± 25.20		22.14 ± 17.99		
Median (25, 75)	17.1 (8.9, 30.6)		16.9 (10, 31)		0.654
Lowest serum SCr, mg/dL					
Mean ± SD	1.02 ± 1.05		0.96 ± 1.03		
Median (25, 75)	0.68 (0.5, 1.06)		0.66 (0.49, 0.96)		0.006
Highest serum SCr, mg/dL					
Mean ± SD	2.81 ± 2.79		2.46 ± 2.67		
Median (25, 75)	1.68 (1.04, 3.3)		1.41 (0.94, 2.61)		0.001
RIFLE category†					
None	81	14.92%	213	18.46%	0.073
Risk	112	20.63%	306	26.52%	0.009
Injury	133	24.49%	247	21.40%	0.154

TABLE 1. *Continued*

	30-Day Readmission = Yes		30-Day Readmission = No		
	N = 543	% = 32.00%	N = 1,154	% = 68.00%	*P* Value
Failure	120	22.10%	212	18.37%	0.071
Loss	50	9.21%	91	7.89%	0.357
End-stage	47	8.66%	85	7.37%	0.355
Infection source‡					
Urine	95	17.50%	258	22.36%	0.021
Abdomen	69	12.71%	113	9.79%	0.070
Lung	93	17.13%	232	20.10%	0.146
Line	91	16.76%	150	13.00%	0.038
CNS	1	0.18%	16	1.39%	0.012
Skin	51	9.39%	82	7.11%	0.102
Unknown	173	31.86%	375	32.50%	0.794

NOTE: **Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CHF, congestive heart failure; CKD, chronic kidney disease; CLD, chronic liver disease; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; HCA, healthcare associated; HIV, human immunodeficiency virus; LOS, length of stay; LTAC, long-term acute care; MV, mechanical ventilation; RF, risk factors; RIFLE, Risk, Injury, Failure, Loss, End-stage; SCr, serum creatinine; SD, standard deviation; TPN, total parenteral nutrition; WBC, white blood cells. *Hospital-acquired BSI defined as BSI that developed after day 2 of hospitalization. †Multiple infection sources possible. ‡RIFLE categories were as follows: Risk = increase in SCr ×1.5; Injury = increase in SCr ×2.0; Failure = increase in SCr ×3.0 or SCr ≥4 mg/dL; Loss = acute renal failure requiring renal replacement therapy temporarily while in the hospital; ESKD = end-stage kidney disease requiring dialysis. If none of these changes was detected, then the patient did not have evidence of acute kidney injury and was designated RIFLE: None.

or Fisher exact test for small samples was used to examine differences between groups. We developed multiple logistic regression models to identify clinical risk factors that were associated with 30-day all-cause readmission. All risk factors that were significant at $\alpha \leq 0.20$ in the univariate analyses, as well as all biologically plausible factors even if they did not reach this level of significance, were included in the models. All variables entered into the models were assessed for collinearity, and interaction terms were tested. The most parsimonious models were derived using the backward manual elimination method, and the best-fitting model was chosen based on the area under the receiver operating characteristics curve (AUROC or the C statistic). The model's calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test. All tests were 2-tailed, and a P value <0.05 represented statistical significance.

All computations were performed in Stata/SE, version 9 (StataCorp, College Station, TX).

Role of Sponsor

The sponsor had no role in the design, analyses, interpretation, or publication of the study.

RESULTS

Among the 1697 patients with severe sepsis or septic shock who were discharged alive from the hospital, 543 (32.0%) required a rehospitalization within 30 days. There were no differences in age or gender distribution between the groups (Table 1). All comorbidities examined were more prevalent among those with a 30-day readmission than among those without, with the median Charlson comorbidity score reflecting this imbalance (5 vs 4, $P < 0.001$). Similarly, most of the HCA risk factors were more prevalent among the readmitted group than the comparator group, with HCA sepsis among 94.2% of the former and 90.7% of the latter ($P = 0.014$).

During the index hospitalization, 589 patients (34.7%) suffered from septic shock requiring vasopressors; this did not impact the 30-day readmission risk (Table 1). Commensurately, markers of severity of acute illness (APACHE II score, mechanical ventilation, peak white blood cell count) did not differ between the groups. With respect to the primary source of sepsis, urine was less, whereas central nervous system was more likely among those readmitted within 30 days. Similarly, there was a significant imbalance between the groups in the prevalence of AKI (Table 1). Specifically, those who did require a readmission were slightly less likely to have sustained no AKI (RIFLE: None; 14.9% vs 18.5%, $P = 0.073$). Those requiring readmission were also less likely to be in the category RIFLE: Risk (20.6% vs 26.5%, $P = 0.009$). The direction of this disparity was reversed for the Injury and Failure categories. No differences between groups were seen among those with categories Loss and end-stage kidney disease (ESKD) (Table 1).

The microbiology of sepsis did not differ in most respects between the 30-day readmission groups, save for several organisms (Table 2). Most strikingly, those who required a readmission were more likely than those who did not to be infected with *Bacteroides* spp, *Candida* spp, an MDR or an ESBL organism (Table 2). As for the outcomes of the index hospitalization, those with a repeat admission had a longer overall and post–onset of sepsis initial hospital length of stay, and were less likely to be discharged either home without home health care or transferred to another hospital at the end of their index hospitalization (Table 3).

TABLE 2. Sepsis Microbiology

	30-Day Readmission = Yes		30-Day Readmission = No		
	N	%	N	%	*P* Value
	543	32.00%	1,154	68.00%	
Gram-positive BSI	260	47.88%	580	50.26%	0.376
Staphylococcus aureus	138	25.41%	287	24.87%	0.810
MRSA	78	14.36%	147	12.74%	0.358
VISA	6	1.10%	9	0.78%	0.580
Streptococcus pneumoniae	7	1.29%	33	2.86%	0.058
Streptococcus spp	34	6.26%	81	7.02%	0.606
Peptostreptococcus spp	5	0.92%	15	1.30%	0.633
Clostridium perfringens	4	0.74%	10	0.87%	1.000
Enterococcus faecalis	54	9.94%	108	9.36%	0.732
Enterococcus faecium	29	5.34%	63	5.46%	1.000
VRE	36	6.63%	70	6.07%	0.668
Gram-negative BSI	231	42.54%	515	44.63%	0.419
Escherichia coli	54	9.94%	151	13.08%	0.067
Klebsiella pneumoniae	54	9.94%	108	9.36%	0.723
Klebsiella oxytoca	11	2.03%	18	1.56%	0.548
Enterobacter aerogenes	6	1.10%	13	1.13%	1.000
Enterobacter cloacae	21	3.87%	44	3.81%	1.000
Pseudomonas aeruginosa	28	5.16%	65	5.63%	0.733
Acinetobacter spp	8	1.47%	27	2.34%	0.276
Bacteroides spp	25	4.60%	30	2.60%	0.039
Serratia marcescens	14	2.58%	21	1.82%	0.360
Stenotrophomonas maltophilia	3	0.55%	8	0.69%	1.000
Achromobacter spp	2	0.37%	3	0.17%	0.597
Aeromonas spp	2	0.37%	1	0.09%	0.241
Burkholderia cepacia	0	0.00%	6	0.52%	0.186
Citrobacter freundii	2	0.37%	15	1.39%	0.073
Fusobacterium spp	7	1.29%	10	0.87%	0.438
Haemophilus influenzae	1	0.18%	4	0.35%	1.000
Prevotella spp	1	0.18%	6	0.52%	0.441
Proteus mirabilis	9	1.66%	39	3.38%	0.058
MDR PA	2	0.37%	7	0.61%	0.727
ESBL	10	6.25%	8	2.06%	0.017
CRE	2	1.25%	0	0.00%	0.028
MDR Gram-negative or Gram-positive	231	47.53%	450	41.86%	0.036
Candida spp	58	10.68%	76	6.59%	0.004
Polymicrobal BSI	50	9.21%	111	9.62%	0.788
Initially inappropriate treatment	119	21.92%	207	17.94%	0.052

NOTE: **Abbreviations:** BSI, blood stream infection; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended spectrum β-lactamase; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus* spp.

In a logistic regression model, 5 factors emerged as predictors of 30-day readmission (Table 4). Having RIFLE: Injury or RIFLE: Failure carried an approximately 2-fold increase in the odds of 30-day rehospitalization (odds ratio: 1.95, 95% confidence interval: 1.30–2.93, $P = 0.001$) relative to having a RIFLE: None or RIFLE: Risk. Although having strong association with this outcome, harboring an ESBL organism or *Bacteroides* spp were both relatively infrequent events (3.3% ESBL and 3.2% *Bacteroides* spp). Infection with *Escherichia coli* and urine as the source of sepsis both appeared to be significantly protective against a readmission (Table 4). The model's discrimination was moderate (AUROC = 0.653) and its calibration adequate (Hosmer-Lemeshow $P = 0.907$). (See Supporting Information, Appendix 1, in the online version of this article for the steps in the development of the final model.)

DISCUSSION

In this single-center retrospective cohort study, nearly one-third of survivors of culture-positive severe sepsis or septic shock required a rehospitalization within 30 days of discharge from their index admission. Factors that contributed to a higher odds of rehospitalization were having mild-to-moderate AKI (RIFLE: Injury or RIFLE: Failure) and infection with ESBL organisms or *Bacteroides* spp, whereas urine as the source of sepsis and *E coli* as the pathogen appeared to be protective.

A recent study by Hua and colleagues examining the New York Statewide Planning and Research Cooperative System for the years 2008 to 2010 noted a 16.2% overall rate of 30-day rehospitalization among survivors of initial critical illness.[11] Just as we observed, Hua et al. concluded that development of AKI correlated with readmission. Because they relied

TABLE 3. Index Hospitalization Outcomes

	30-Day Readmission = Yes		30-Day Readmission = No		
	N = 543	% = 32.00%	N = 1,154	% = 68.00%	*P* Value
Hospital LOS, days					
Mean ± SD	26.44 ± 23.27		23.58 ± 21.79		0.019
Median (25, 75)	19.16 (9.66, 35.86)		17.77 (8.9, 30.69)		
Hospital LOS following BSI onset, days					
Mean ± SD	19.80 ± 18.54		17.69 ± 17.08		0.022
Median (25, 75)	13.9 (7.9, 25.39)		12.66 (7.05, 22.66)		
Discharge destination					
Home	125	23.02%	334	28.94%	0.010
Home with home care	163	30.02%	303	26.26%	0.105
Rehab	81	14.92%	149	12.91%	0.260
LTAC	41	7.55%	87	7.54%	0.993
Transfer to another hospital	1	0.18%	19	1.65%	0.007
SNF	132	24.31%	262	22.70%	0.465

NOTE: **Abbreviations:** BSI, bloodstream infection; LOS, length of stay; LTAC, long-term acute care; SD, standard deviation; SNF, skilled nursing facility.

TABLE 4. Predictors of 30-Day Readmission*

	OR	95% CI	*P* Value
ESBL	4.503	1.429–14.190	0.010
RIFLE: Injury or Failure (reference: RIFLE: None or Risk)	1.951	1.297–2.933	0.001
Bacteroides spp	2.044	1.058–3.948	0.033
Source: urine	0.583	0.347–0.979	0.041
Escherichia coli	0.494	0.270–0.904	0.022

NOTE: Area under the receiver operating characteristics curve = 0.653. Hosmer-Lemeshow $P = 0.907$.

*Covariates not retained at $P < 0.05$.

Baseline characteristics of patients at index hospitalization: race, admitted from home, prior antibiotics, prior bacteremia, transfer from another hospital, immune suppression, hemodialysis, prior bacteremia. Sepsis-related parameters during the index hospitalization: central line, total parenteral nutrition, Surgery: none, Surgery: abdominal, lowest serum creatinine, highest serum creatinine, RIFLE: None, Source: central nervous system, Source: skin, Source: intra-abdominal, Source: lung. Sepsis microbiology: *Streptococcus pneumoniae*, *Proteus mirabilis*, multidrug resistance among Gram-negatives, initially inappropriate antibiotic treatment. Index hospitalization outcomes: discharged home, discharged home with home care, transferred to another hospital, hospital length of stay. Factors dropped for collinearity: Individual comorbidities, *Candida* spp, hospital length of stay following the onset of sepsis. **Abbreviations:** CI, confidence interval; ESBL, extended spectrum β-lactamase; OR, odds ratio; RIFLE, Risk, Injury, Failure, Loss, End-stage.

on administrative data for their analysis, AKI was diagnosed when hemodialysis was utilized. Examining AKI using SCr changes, our findings add a layer of granularity to the relationship between AKI stages and early readmission. Specifically, we failed to detect any rise in the odds of rehospitalization when either very mild (RIFLE: Risk) or severe (RIFLE: Loss or RIFLE: ESKD) AKI was present. Only when either RIFLE: Injury or RIFLE: Failure developed did the odds of readmission rise. In addition to diverging definitions between our studies, differences in populations also likely yielded different results.[11] Although Hua et al. examined all admissions to the ICU regardless of the diagnosis or illness severity, our cohort consisted of only those ICU patients who survived culture-positive severe sepsis/septic shock. Because AKI is a known risk factor for mortality in sepsis,[19] the potential for immortal time bias leaves a smaller pool of surviving patients with ESKD at risk for readmission. Regardless of the explanation, it may be prudent to focus on preventing AKI not only to improve survival, but also from the standpoint of diminishing the risk of an early readmission.

Four additional studies have examined the frequency of early readmissions among survivors of critical illness. Liu et al. noted 17.9% 30-day rehospitalization rate among sepsis survivors.[12] Factors associated with the risk of early readmission included acute and chronic diseases burdens, index hospital LOS, and the need for the ICU in the index sepsis admission. In contrast to our cohort, all of whom were in the ICU during their index episode, less than two-thirds of the entire population studied by Liu had required an ICU admission. Additionally, Liu's study did not specifically examine the potential impact of AKI or of microbiology on this outcome.

Prescott and coworkers examined healthcare utilization following an episode of severe sepsis.[13] Among other findings, they reported a 30-day readmission rate of 26.5% among survivors. Although closer to our estimate, this study included all patients surviving a severe sepsis hospitalization, and not only those with a positive culture. These investigators did not examine predictors of readmission.[13]

Horkan et al. examined specifically whether there was an association between AKI and postdischarge outcomes, including 30-day readmission risk, in a large cohort of patients who survived their critical illness.[20] In it they found that readmission risk ranged from 19% to 21%, depending on the extent of the AKI. Moreover, similar to our findings, they reported that in an adjusted analysis RIFLE: Injury and RIFLE: Failure were associated with a rise in the odds of a 30-day rehospitalizaiton. In contrast to our study,

Horkan et al. did detect an increase in the odds of this outcome associated with RIFLE: Risk. There are likely at least 3 reasons for this difference. First, we focused only on patients with severe sepsis or septic shock, whereas Horkan and colleagues included all critical illness survivors. Second, we were able to explore the impact of microbiology on this outcome. Third, Horkan's study included an order of magnitude more patients than did ours, thus making it more likely either to have the power to detect a true association that we may have lacked or to be more susceptible to type I error.

Finally, Goodwin and colleagues utilized 3 states' databases included in the Health Care and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality to study frequency and risk factors for 30-day readmission among survivors of severe sepsis.[21] Patients were identified based on the use of the severe sepsis (995.92) and septic shock (785.52). These authors found a 30-day readmission rate of 26%. Although chronic renal disease, among several other factors, was associated with an increase in this risk, the data source did not permit these investigators to examine the impact of AKI on the outcomes. Similarly, HCUP data do not contain microbiology, a distinct difference from our analysis.

If clinicians are to pursue strategies to reduce the risk of an all-cause 30-day readmission, the key goal is not simply to identify all variables associated with readmission, but to focus on factors that are potentially modifiable. Although neither Hua nor Liu and their teams identified any additional factors that are potentially modifiable,[11,12] in the present study, among the 5 factors we identified, the development of mild to moderate AKI during the index hospitalization may deserve stronger consideration for efforts at prevention. Although one cannot conclude automatically that preventing AKI in this population could mitigate some of the early rehospitalization risk, critically ill patients are frequently exposed to a multitude of nephrotoxic agents. Those caring for subjects with sepsis should reevaluate the risk-benefit equation of these factors more cautiously and apply guideline-recommended AKI prevention strategies more aggressively, particularly because a relatively minor change in SCr resulted in an excess risk of readmission.[22]

In addition to AKI, which is potentially modifiable, we identified several other clinical factors predictive of 30-day readmission, which are admittedly not preventable. Thus, microbiology was predictive of this outcome, with *E coli* engendering fewer and *Bacteroides spp* and ESBL organisms more early rehospitalizations. Similarly, urine as the source of sepsis was associated with a lower risk for this endpoint.

Our study has a number of limitations. As a retrospective cohort, it is subject to bias, most notably a selection bias. Specifically, because the flagship hospital of the BJC HealthCare system is a referral center, it is possible that we did not capture all readmissions. However, generally, if a patient who receives healthcare within 1 of the BJC hospitals presents to a nonsystem hospital, that patient is nearly always transferred back into the integrated system because of issues of insurance coverage. Analysis of certain diagnosis-related groups has indicated that 73% of all patients overall discharged from 4 of the large BJC system institutions who require a readmission within 30 days of discharge return to a BJC hospital (personal communication, Financial Analysis and Decision Support Department at BJC to Dr. Kollef May 12, 2015). Therefore, we may have misclassified the outcome in as many as 180 patients. The fact that our readmission rate was fully double that seen in Hua et al.'s and Liu et al.'s studies, and somewhat higher than that reported by Prescott et al., attests not only to the population differences, but also to the fact that we are unlikely to have missed a substantial percentage of readmissions.[11–13] Furthermore, to mitigate biases, we enrolled all consecutive patients meeting the predetermined criteria. Missing from our analysis are events that occurred between the index discharge and the readmission. Likewise, we were unable to obtain such potentially important variables as code status or outpatient mortality following discharge. These intervening factors, if included in subsequent studies, may increase the predictive power of the model. Because we relied on administrative coding to identify cases of severe sepsis and septic shock, it is possible that there is misclassification within our cohort. Recent studies indicate, however, that the Angus definition, used in our study, has high negative and positive predictive values for severe sepsis identification.[23] It is still possible that our cohort is skewed toward a more severely ill population, making our results less generalizable to the less severely ill septic patients.[24] The study was performed at a single healthcare system and included only cases of severe sepsis or septic shock that had a positive blood culture, and thus the findings may not be broadly generalizable either to patients without a positive blood culture or to institutions that do not resemble it.

In summary, we have demonstrated that survivors of culture-positive severe sepsis or septic shock have a high rate of 30-day rehospitalization. Because the US federal government's initiatives deem 30-day readmissions to be a quality metric and penalize institutions with higher-than average readmission rates, a high volume of critically ill patients with culture-positive severe sepsis and septic shock may disproportionately put an institution at risk for such penalties. Unfortunately, not many of the determinants of readmission are amenable to prevention. As sepsis survival continues to improve, hospitals will need to concentrate their resources on coordinating care of these complex patients so as to improve both

individual quality of life and the quality of care that they provide.

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