ORIGINAL ARTICLE

Predictors of Hospital-Acquired Urinary Tract–Related Bloodstream Infection

M. Todd Greene, PhD, MPH;[1,2] Robert Chang, MD;[1,2] Latoya Kuhn, MPH;[2,3] Mary A. M. Rogers, PhD;[1,2] Carol E. Chenoweth, MD;[4,5] Emily Shuman, MD;[4] Sanjay Saint, MD, MPH[2,3,1]

OBJECTIVE. Bloodstream infection (BSI) secondary to nosocomial urinary tract infection is associated with substantial morbidity, mortality, and additional financial costs. Our objective was to identify predictors of nosocomial urinary tract–related BSI.

DESIGN. Matched case-control study.

SETTING. Midwestern tertiary care hospital.

PATIENTS. Cases ($n = 298$) were patients with a positive urine culture obtained more than 48 hours after admission and a blood culture obtained within 14 days of the urine culture that grew the same organism. Controls ($n = 667$), selected by incidence density sampling, included patients with a positive urine culture who were at risk for BSI but did not develop one.

METHODS. Conditional logistic regression and classification and regression tree analyses.

RESULTS. The most frequently isolated microorganisms that spread from the urinary tract to the bloodstream were *Enterococcus* species. Independent risk factors included neutropenia (odds ratio [OR], 10.99; 95% confidence interval [CI], 5.78–20.88), renal disease (OR, 2.96; 95% CI, 1.98–4.41), and male sex (OR, 2.18; 95% CI, 1.52–3.12). The probability of developing a urinary tract–related BSI among neutropenic patients was 70%. Receipt of immunosuppressants (OR, 1.53; 95% CI, 1.04–2.25), insulin (OR, 4.82; 95% CI, 2.52–9.21), and antibacterials (OR, 0.66; 95% CI, 0.44–0.97) also significantly altered risk.

CONCLUSIONS. The heightened risk of urinary tract–related BSI associated with several comorbid conditions suggests that the management of nosocomial bacteriuria may benefit from tailoring to certain patient subgroups. Consideration of time-dependent risk factors, such as medications, may also help guide clinical decisions in reducing BSI.

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Urinary tract infection (UTI) is the most frequent healthcare-associated infection in the United States.[1] Although bloodstream infection (BSI) secondary to healthcare-associated UTI occurs in only 1%–4% of cases,[2] mortality rates among patients with urinary tract–related BSI may be as high as 33%.[3] The economic consequences of treating urinary tract–related BSI are also sizeable. A previous economic analysis estimated that each episode of BSI originating from a urinary tract source is expected to cost at least an additional $2,836[2] (equivalent to $3,744 per episode after adjustment for inflation to 2011). Despite recent renewed interest in healthcare-associated UTI, in part due to the decision by the Centers for Medicare and Medicaid Services to no longer reimburse hospitals for catheter-associated UTI not present on admission,[4] surprisingly little is known about the epidemiology of nosocomial urinary tract–related BSI.

Previously identified risk factors include age,[2,5] male sex,[2,6] indwelling urethral catheters,[5,7] obstructive urologic disease,[5] immunosuppressant therapy,[2] malignancy,[2] elevated serum creatinine,[8] low serum albumin,[8] diabetes mellitus,[2,8] and cigarette use.[2] However, these findings are limited due to a paucity of studies investigating potential predictors for urinary tract–related BSI. Elucidating potential predictors of nosocomial urinary tract–related BSI could help define proper infection control practices and enhance the safety of hospitalized patients. We therefore conducted a matched case-control study of adult patients hospitalized in the University of Michigan Medical Center from January 1, 2000, through

Affiliations: 1. Division of General Medicine, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan; 2. Department of Veterans Affairs/University of Michigan Patient Safety Enhancement Program, Department of Veterans Affairs Hospital, Ann Arbor, Michigan; 3. Center for Practice Management and Outcomes Research, Ann Arbor Department of Veterans Affairs Health Services Research and Development Center of Excellence, Department of Veterans Affairs Hospital, Ann Arbor, Michigan; 4. Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan; 5. Department of Infection Control and Epidemiology, University of Michigan Health System, Ann Arbor, Michigan.

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September 30, 2008, to examine both previously identified and novel risk factors that may alter the risk of urinary tract–related BSI.

METHODS

Setting

The University of Michigan Medical Center is a tertiary referral center located in southeastern Michigan that has more than 800 beds and 99 intensive care unit (ICU) beds. This study was approved by the University of Michigan Health System Institutional Review Board.

Case Definition

All adults (21 or more years of age) with (*a*) a positive urine and blood culture with the same microorganism during their hospital stay, (*b*) the urine culture being obtained prior to or on the same day as the blood culture, (*c*) the positive urine culture not being obtained within the first 2 days of admission, and (*d*) the blood culture obtained within 14 days of the urine culture were included in our case series. A urine culture was defined as positive if more than 10^3 colony-forming units (CFUs)/mL of a single organism grew. Manual record review for all cases was performed by physician reviewers (E.S., R.C., and C.E.C.) to identify and exclude cases with evidence of primary BSI with hematogenous spread of infection to the kidney (eg, central line–associated BSI and endocarditis).

Control Selection

Controls were selected by incidence density sampling and included adults with a positive urine culture who were at risk for a BSI but did not develop one during their hospital stay. Our explicit goal was to identify factors that influenced the spread of a urinary tract microorganism to the bloodstream, and as such controls did not have a positive blood culture; controls had either a negative blood culture or no blood culture ordered. Controls were matched to each case by calendar time (within 120 days) when the BSI occurred in that case. Under this design, a case's exposure history was assessed up to the time that the BSI occurred, and the exposure history of the respective matched control(s) was assessed up to an analogous index time.[9] For example, if the urinary tract–related BSI occurred on the 20th day after hospital admission for the case, a similar period was evaluated for the matched control (admission to the 20th day of hospitalization). For purposes of this investigation, this day was labeled the "index date."

Microbiological Techniques

All urine and blood cultures were ordered and collected at the clinical discretion of healthcare providers. Blood cultures were collected and incubated using BacT/Alert FA and FN (bioMérieux), and conventional microbiological methods were used for identification of microorganisms from blood and urine cultures.

Data Collection

Demographic, clinical, and microbiological information was extracted from electronic medical records, with additional medical chart reviews performed by physician reviewers (R.C., E.S., and C.E.C.). Cigarette use was dichotomized as ever versus never smoker. Coexisting conditions were defined by the presence of *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. Neutropenia was defined by laboratory values (neutrophil count less than 500 cells/μL). Daily inpatient medication administration data were used to generate dichotomous variables for medication use during the 2 days prior to the index date.

Statistical Analysis

Means and standard deviations for continuous variables and frequencies and percentages for categorical variables were used to summarize patient characteristics. Continuous variables were compared using standard t tests, and categorical variables were compared using the χ^2 statistic. Conditional logistic regression models were fit to assess unadjusted and adjusted associations between predictor variables and urinary tract–related BSI while accounting for the matched design. Additionally, we used classification and regression tree (CART) methods[10] as a means of identifying high-risk population subgroups. We set α at .05, 2-tailed. Descriptive and conditional logistic regression analyses were conducted using Stata/SE 11 (StataCorp), and the CART analysis was conducted in R using the RPART package.

RESULTS

Descriptive

Of the 355 patients meeting the case definition, 57 were deemed to have primary BSI (after review performed by 2 physicians, with any disagreements resolved via adjudication by a third physician), leaving a total of 298 eligible cases in these analyses. A total of 64% of female cases and 71% of male cases had urine culture values of 10^5 CFUs/mL or higher. The distribution of the time between urine and blood culture collection among the cases was as follows: same day, 58%; 1 day, 11%; and 2 or more days, 31%. A total of 667 controls were selected and included, with case-control ratios within matched sets ranging from 1 : 1 to 1 : 4. Descriptive characteristics of the patients are displayed in Table 1. Cases were younger than controls ($P = .003$), were more likely to be male ($P < .001$), and had longer average lengths of stay ($P < .001$). Cases were also more likely to have renal disease ($P < .001$), liver disease ($P < .001$), cancer ($P < .001$), and neutropenia ($P < .001$). The median time between admission and BSI among the cases was 15 days. Approximately one-third of patients who developed urinary tract–related BSI

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TABLE 1. Descriptive Characteristics of Cases and Controls, 2000–2008

Characteristic	Cases (n = 298)	Controls (n = 667)	P
Age, mean ± SD, years	58.1 ± 15.3	61.3 ± 14.9	.003
LOS, mean ± SD, days	41.3 ± 35.7	26.2 ± 21.6	<.001
Male	164 (55)	252 (38)	<.001
Cigarette use	140 (47)	292 (44)	.393
Diabetes	69 (23)	164 (25)	.690
Hypertension	130 (44)	349 (52)	.015
Renal disease	153 (51)	178 (27)	<.001
Liver disease	52 (17)	46 (7)	<.001
Malignancy	121 (41)	165 (25)	<.001
Urologic procedure	37 (12)	30 (5)	<.001
Neutropenia	67 (22)	29 (4)	<.001
Immunosuppressive therapy	136 (46)	145 (22)	<.001
Antibacterial therapy	158 (53)	382 (57)	.247
Insulin	33 (11)	25 (4)	<.001

NOTE. Data are no. (%), unless otherwise indicated. Results displayed for pharmacologic therapies were therapies that were administered during the hospital stay 2 days prior to the index date. The index date is the bloodstream infection date of the case within each matched case-control set. LOS, length of stay; SD, standard deviation.

(32.2%) died while in the hospital, compared with 4.5% of the controls ($P < .001$).

The distributions of microorganisms identified in the cases and controls are illustrated in Table 2. *Enterococcus* species were the most common microorganisms isolated in both cases and controls and were isolated more frequently in cases than in controls ($P = .011$). Coagulase-positive staphylococcus was also isolated more frequently in cases ($P < .001$), whereas *Klebsiella* species were isolated more frequently in controls ($P = .04$).

Conditional Logistic Regression

Statistically significant odds ratios (ORs) and 95% confidence intervals (CIs) from the fully adjusted conditional logistic regression model are provided in Table 3. After adjusting for age, diabetes mellitus, numerous comorbidities, and certain medications administered during the hospital stay, the odds of developing urinary tract–related BSI were twice as high in men than in women ($P < .001$). Neutropenia, renal disease, and liver disease were among the strongest comorbid predictors of urinary tract–related BSI, increasing the odds approximately 11-fold ($P < .001$), 3-fold ($P < .001$), and more than 2-fold ($P = .003$), respectively.

Although we did not detect a significant effect due to diabetes mellitus, we observed nearly a 5-fold increase in risk of urinary tract–related BSI among patients given insulin ($P < .001$). Intensive insulin therapy in the ICU has been shown to reduce mortality and morbidity,[11] including reductions in bloodstream and other nosocomial infections.[12] We separately tested for the interaction between insulin therapy and ICU status and found that, while the direction and significance of the main effect of insulin remained, the insulin effect was not dependent on ICU status (interaction OR, 1.19; 95% CI, 0.11–13.2; $P = .89$).

We also detected a number of time-dependent treatment factors that may reduce the risk of urinary tract–related BSI. For example, antibacterial therapy conferred a protective effect against the development of urinary tract–related BSI (OR, 0.66; 95% CI, 0.44–0.97). In unadjusted models, statin therapy demonstrated a statistically significant protective effect against the odds of developing a urinary tract–related BSI (OR, 0.56; 95% CI, 0.39–0.82). Although the direction of the effect persisted in our fully adjusted model, it was no longer statistically significant (OR, 0.85; 95% CI, 0.51–1.41).

Classification and Regression Trees

Variables for inclusion in the CART model were informed by theory and included all covariates in the fully adjusted conditional logistic regression model as well as time to BSI in cases and dichotomous variables for the 3 most commonly detected microorganisms in the study sample (ie, *Enterococcus* species, *Candida* species, and *Escherichia coli*). The CART procedure revealed that the 6 best discriminators for urinary tract–related BSI were neutropenia, renal disease, inpatient insulin administration, urologic procedure, liver disease, and age at admission (Figure 1). Neutropenic patients defined the first subgroup (terminal node 1), and the probability of having urinary tract–related BSI among neutropenic patients was 70%. The subgroup of patients with renal disease who were given insulin 2 days prior to the index date (terminal node 3) also had a 70% probability of having urinary tract–related BSI. Other key subgroups identified were patients with renal disease and urologic procedure (terminal node 4; 61.3% prob-

TABLE 2. Distribution of Microorganisms among Cases and Controls, 2000–2008

Microorganism	Cases (n = 298)	Controls (n = 667)	P
Enterococcus species	90 (30.2)	149 (22.3)	.011
Candida species	50 (16.8)	146 (21.9)	.082
Escherichia coli	41 (13.8)	123 (18.4)	.090
Coagulase-positive staphylococcus	27 (9.1)	17 (2.6)	<.001
Pseudomonas species	23 (7.7)	48 (7.2)	.878
Coagulase-negative staphylococcus	17 (5.7)	27 (4.1)	.331
Klebsiella species	17 (5.7)	67 (10.0)	.037
Enterobacter species	14 (4.7)	30 (4.5)	1.000
Proteus species	5 (1.7)	17 (2.6)	.546
Citrobacter species	4 (1.3)	5 (0.8)	.601
Acinetobacter species	3 (1.0)	2 (0.3)	.353
Streptococcus species	3 (1.0)	11 (1.6)	.631
Other[a]	4 (1.3)	21 (3.1)	.158
Unspecified	...	4 (0.6)	...

NOTE. Data are no. (%).

[a] Includes *Elizabethkingae*, *Morganella*, and *Serratia* species.

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TABLE 3. Significant Predictors of Nosocomial Urinary Tract–Related Bloodstream Infection

Predictor variable	OR (95% CI)
Neutropenia	10.99 (5.78–20.88)
Insulin	4.82 (2.52–9.21)
Renal disease	2.96 (1.98–4.41)
Urologic procedure	2.49 (1.31–4.73)
Liver disease	2.34 (1.35–4.06)
Male sex	2.18 (1.52–3.12)
Immunosuppressive therapy	1.53 (1.04–2.25)
Antibacterial therapy	0.66 (0.44–0.97)

NOTE. Odds ratios (ORs) are from a multivariable conditional logistic regression analysis and were adjusted for all other covariates presented as well as age, diabetes mellitus, ever versus never cigarette smoking, hypertension, intensive care unit status 2 days prior to the index date, and statin therapy. All pharmacologic therapies modeled were therapies that were administered during the hospital stay 2 days prior to the index date. The index date is the bloodstream infection date of the case within each matched case-control set. CI, confidence interval.

ability), and patients more than 51.5 years of age with both renal and liver disease (terminal node 7; 62.5% probability).

DISCUSSION

Few studies have evaluated the epidemiology of patients who develop nosocomial BSI from a urinary source. A previous case-control study of patients with febrile UTI found that the 80 patients with BSI were older and more frequently had an indwelling urethral catheter in place or obstructive urologic disease compared with the 88 patients without BSI.[5] Krieger et al[6] evaluated a prospective cohort of 40,718 patients, identifying 565 cases of nosocomial BSI (32 of which were felt to have originated from the urinary tract), and they identified male sex and infection with *Serratia marcescens* as risk factors for BSI. More recently, Saint et al[2] conducted a case-control study and identified 95 cases with concordant positive blood and urine cultures more than 48 hours after admission, matched with 142 controls with only positive urine cultures more than 48 hours after admission. Risk factors for urinary tract–related BSI included immunosuppressant therapy within 14 days of bacteriuria, malignancy, male sex, and cigarette use within 5 years. Age-dependent effects were also detected, including the presence of diabetes mellitus, which conferred increased risk in patients more than 70 years old.

In our study, we were able to more fully explore the extent to which a number of previously identified risk factors may alter the risk of developing urinary tract–related BSI. While women generally have a greater risk of developing UTI,[13] we found that men were more likely than women to develop urinary tract–related BSI. While gender is clearly a nonmodifiable risk factor, this result supports previous findings[2,6] and suggests that strategies to prevent the development of BSI from a urinary source may need to be gender specific.

Diabetes mellitus is an extremely important cause of morbidity and mortality in the United States, affecting more than 25 million US adults in 2010.[14] Individuals with diabetes mellitus may have elevated risks for a number of infections (including UTI) due to altered aspects of the immune system.[15] Although we did not find diabetes mellitus to confer an increased risk toward the development of urinary tract–related BSI, we did detect an increased risk among patients who received insulin. A recent study investigating the influence of blood glucose levels among persons with diabetes mellitus on the risk of BSI found that short-term blood glucose levels of 110 to 139 mg/dL were associated with a 2-fold increased risk of BSI.[16] With the administration of insulin (within 2 days prior to the index date) used as a proxy for short-term hyperglycemia, the results of our study are consistent with this phenomenon. Although it remains unclear whether short-term hyperglycemia is an effect of BSI rather than a contributing cause, elevated blood glucose levels may be an indicator of nosocomial BSI risk.[16]

Our study extends prior work by detecting several significant associations between a number of novel and time-dependent risk factors and urinary tract–related BSI. Although previous studies have shown the relationship between malignancy and urinary tract–related BSI,[2] to our knowledge none have assessed the potential role of neutropenia explicitly. With a sensitive definition of severe neutropenia based on confirmed laboratory values used, approximately 20% of all neutropenic patients in our study did not have positive histories of malignancy. Severe neutropenia increases the risk and severity of bacterial and fungal infections.[17] In our investigation, 70% of neutropenic patients with UTI developed BSI. Other investigators have shown that as many as 30% of neutropenic patients develop BSI[18] and may develop BSI an average of 2 days earlier than their nonneutropenic counterparts.[19] Urine cultures are typically obtained from febrile neutropenic patients and may demonstrate asymptomatic bacteriuria. Although treatment for asymptomatic bacteriuria is typically not indicated for many patient subgroups, treatment may be appropriate in neutropenic patients given the high probability of developing urinary tract–related BSI in our study. UTI treatment recommendations may need to specifically address tailored approaches to the management of neutropenic patients.

Consistent with prior work suggesting that high serum creatinine and low serum albumin each confer an increased risk of BSI in patients with UTI,[8] we found that patients with renal and liver disease were more likely to develop urinary tract–related BSI. The increased risk of BSI among patients with chronic kidney disease (CKD) receiving hemodialysis has been described and is in part attributable to the necessary and repeated vascular access.[20] Recently, James et al[21] described a similar increased risk of BSI among CKD patients not receiving hemodialysis. Although the mechanisms contributing to increased susceptibility to infection among CKD patients are not completely understood, it is possible that

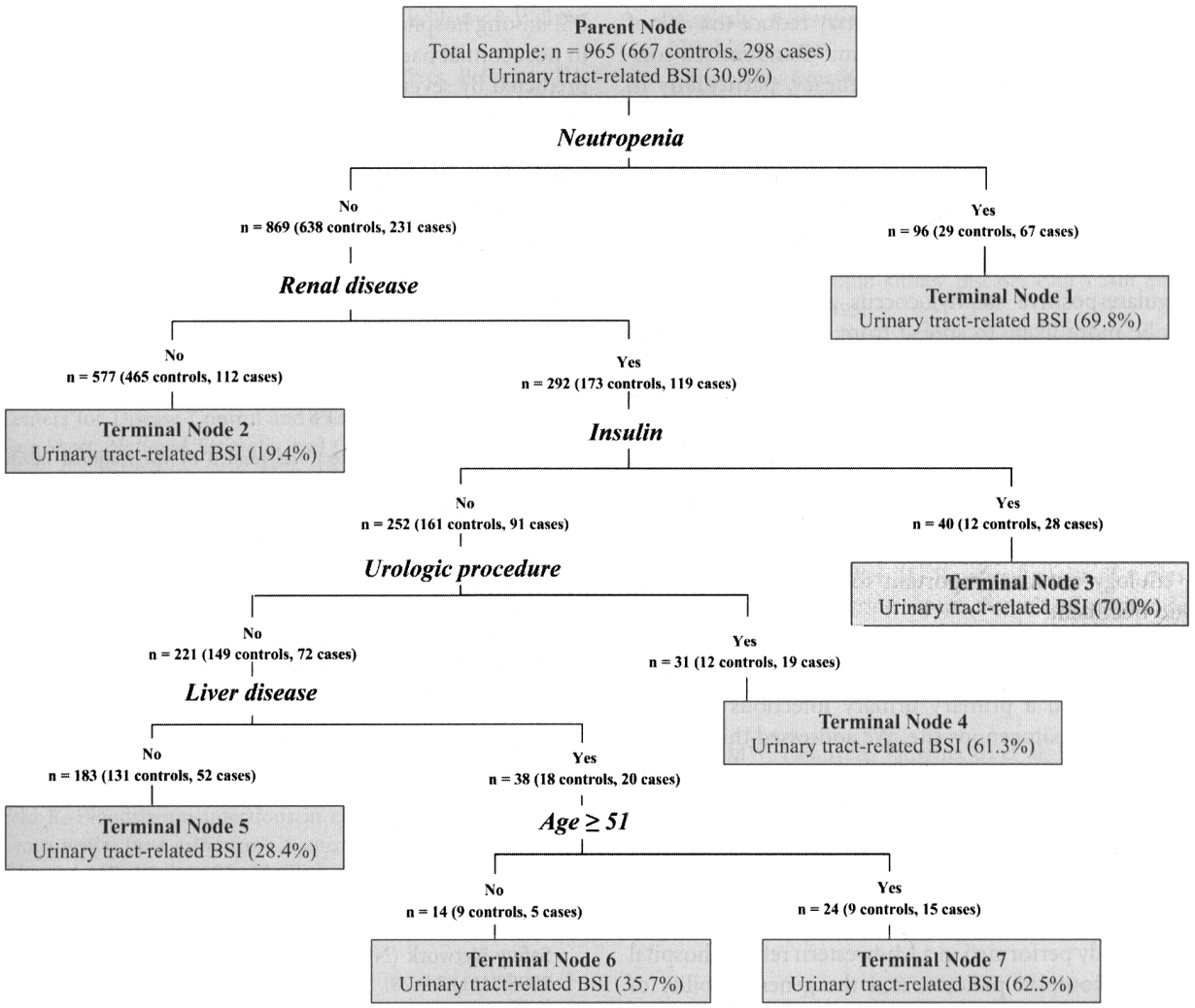

FIGURE 1. High-risk patient subgroups identified by classification and regression tree analysis. BSI, bloodstream infection.

renal dysfunction is a marker for other conditions that increase host susceptibility.[21,22] Alternately, it has been suggested that consequences of CKD (eg, malnutrition, chronic inflammation, and impaired immune function) may partially explain the association between CKD and increased risk of infection.[21-23] Renal failure occurs in approximately 50% of end-stage liver disease patients, and the risk of mortality in such patients is increased, particularly in those with bacterial infections and hepatorenal syndrome.[24] Our nonparametric CART model further suggests that patients with both renal and liver disease are at increased risk of developing urinary tract–related BSI, emphasizing the importance of careful infection management among this high-risk subgroup.

To our knowledge, only 1 previous study[2] has examined how time-dependent medication use alters the risk of urinary tract–related BSI. Our study expands on this previous work by examining a wide range of medications administered at various time points during the hospital stay. We ultimately chose to investigate the influence of medication use during a relatively short time frame (2 days) preceding the index date, during which respective pharmacodynamic and pharmacokinetic properties of various drugs would potentially act to influence the risk of progression to BSI. We found that a number of medications administered within this time frame may alter the risk of BSI progression. For example, immunosuppressant use was associated with an increased risk of BSI, whereas antibacterial use was associated with a reduced risk; these findings are consistent with those of previous work.[2]

Our findings regarding time-dependent statin use contribute to a growing body of literature investigating the potential effects that statins may have on infection risk. Although commonly prescribed for their lipid-lowering effects, statins have pleiotropic immunomodulatory properties, including improved endothelial and microvascular function, anti-inflammatory activity, and increased expression of endothelial nitric

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oxide synthase.[25-28] A recent review of data from observational human studies concluded that statins may reduce the risk of sepsis in patients with bacterial infection.[29] Randomized controlled trials are necessary to assess efficacy, particularly in this era of increasing antibiotic resistance.

We have previously described the microbial etiology of the patients who developed urinary tract–related BSI in our hospital-based sample as well as temporal changes in the microorganisms isolated from these nosocomial infections.[3] Our investigation provides new evidence that *Enterococcus* species and coagulase-positive staphylococcus are microorganisms that may be more likely to spread from the urinary tract to the bloodstream. It is possible that the differences in the growth of certain microorganisms between cases and controls are reflective of selective pressure of empiric antibiotic treatment. Despite this, we did not find a difference in the frequency of antibacterial use between cases and controls. Although the underlying biological reasons for these findings could not be established in our study, understanding the microbial etiology remains important for decisions regarding antibiotic treatment.

Our study has several limitations. First, the retrospective nature of our study affected our ability to determine whether bacteriuria reflected a primary urinary infectious nidus or seeding from a hematogenous site. We addressed this by conducting manual chart reviews and excluding cases felt to have a clear competing bloodstream infectious source. Second, we did not examine the adequacy of antimicrobial therapies. Third, we did not confirm that isolates from the urine and blood were identical organisms by using antimicrobial resistance patterns or molecular typing methods. Fourth, this was a single-site study performed in a Midwestern referral hospital that cares for complex patients, and the generalizability of our findings may be limited. Fifth, we were unable to consistently determine certain variables through administrative or clinical records. Of note, we were not able to obtain reliable data on the presence of urinary catheters. We do not have reason to believe that the proportions of urinary catheters would be significantly different between cases and controls, since all study subjects were required to have nosocomial bacteriuria, which is associated with urinary catheters in most patients. Still, failure to account for this (and other) potential confounding variables may have impacted our results. Finally, it should be noted that the associations between a number of the comorbid conditions and urinary tract–related BSI may be reflective of markers of severity of illness among the cases relative to the controls rather than direct causal (and biologically plausible) links between "exposure" and urinary tract–related BSI. Additionally, while BSI likely contributed to higher mortality among cases relative to controls, we cannot rule out mortality attributable to other comorbid conditions. Nonetheless, such markers may prove valuable in helping guide infection prevention strategies.

Limitations notwithstanding, our study has helped develop a deeper understanding of the etiology of urinary tract–related BSI among hospitalized patients. The likelihood of BSI related to nosocomial bacteriuria among hospitalized patients can be predicted by several host-specific factors, and the heightened risk of urinary tract–related BSI associated with several comorbid conditions suggests that the management of nosocomial bacteriuria should perhaps be tailored to certain patient subgroups. Considering time-dependent risk factors, including inpatient medications, may also help guide clinical decisions in reducing this critical and costly patient safety problem.

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Address correspondence to M. Todd Greene, PhD, MPH, University of Michigan Health System, 2800 Plymouth Road, Building 16–Room 470C, Ann Arbor, MI 48109 (mtgreene@med.umich.edu).

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