



Published in final edited form as:

Infect Control Hosp Epidemiol. 2012 October ; 33(10): 1001–1007. doi:10.1086/667731.

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, MD⁴, and Sanjay Saint, MD, MPH^{1,2,3}

¹Division of General Medicine, Department of Internal Medicine, the University of Michigan Health System, Ann Arbor, Michigan

²Department of Veterans Affairs/University of Michigan Patient Safety Enhancement Program, Department of Veterans Affairs Hospital, Ann Arbor, Michigan

³Center 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

⁴Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan

⁵Department of Infection Control and Epidemiology, University of Michigan Health System, Ann Arbor, Michigan

Abstract

Objective—Bloodstream infection (BSI) secondary to nosocomial urinary tract infection (UTI) 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 > 48 hours after admission and a blood culture obtained within 14 days of the urine culture which 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 (CART) analyses.

Results—The most frequently isolated microorganisms which spread from the urinary tract to the bloodstream were *Enterococcus sp.* Independent risk factors included neutropenia (OR = 10.99, 95% 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.

Corresponding Author: M. Todd Greene, PhD, MPH, University of Michigan Health System, 300 N Ingalls, 7A22, Ann Arbor, Michigan 48109, Fax: (734) 936-5216, Telephone: (734) 936-4795, mtgreene@med.umich.edu.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

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.

Introduction

Urinary tract infection (UTI) is the most frequent healthcare-associated infection in the United States (US).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 \$2,836² (equivalent to \$3,744 per episode after inflation adjustment to 2011). Despite recent renewed interest in healthcare-associated UTI, in part due to the decision by the Centers for Medicare and Medicaid Services (CMS) to no longer reimburse hospitals for catheter-associated UTI not present upon 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 on adult patients hospitalized in the University of Michigan Medical Center from 1 January 2000 through 30 September 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 with 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 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 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 $> 10^3$ CFU/ml of a single organism grew. Manual record review for all cases was performed by physician reviewers (ES, RC, CC) to identify and exclude cases with evidence of primary BSI with hematogenous spread of infection to the kidney (e.g., central line-associated BSI, endocarditis).

Control Selection

Controls were selected by incidence density sampling and included adults with a positive urine culture who were at risk of 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 respective matched control(s) exposure history 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 in the matched control (admission to 20th day of hospitalization). For purposes of this investigation, this day was labeled the "index date."

Microbiological Techniques

All urinary and blood cultures were ordered and collected at the clinical discretion of health care providers. Blood cultures were collected and incubated using BacT/Alert FA and FN (bioMerieux; Durham, North Carolina), 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 (RC, ES, CC). Cigarette use was dichotomized as "ever" versus "never" smoker. Coexisting conditions were defined by the presence of ICD-9-CM codes. Neutropenia was defined by laboratory values (neutrophil count < 500 cells/ μ L). 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 (SD) for continuous variables, and frequencies and percentages for categorical variables, were used to summarize the 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) methods¹⁰ as a means of identifying high-risk population subgroups. Alpha was set at 0.05, 2-tailed. Descriptive and conditional logistic regression analyses were conducted using Stata/SE 11 (College Station, TX), and the CART analysis was conducted in R using the "RPART" package.

Results

Descriptive

Of the 355 patients meeting the case definition, 57 patients were deemed to have primary BSI (after review performed by 2 physicians with any disagreements resolved by adjudication by a third physician), leaving a total of 298 eligible cases in these analyses. A total of 64% of female case patients and 71% of male cases had urine culture values $\geq 10^5$ CFU/ml. The distribution of the time between urine and blood culture collection among the cases was as follows: same day (58%), one day (11%), 2 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 ($p = 0.003$), were more likely to be male ($p < 0.001$), and had longer average lengths of stay ($p < 0.001$). Cases were also more likely to have renal disease

($p < 0.001$), liver disease ($p < 0.001$), cancer ($p < 0.001$) and neutropenia ($p < 0.001$). The median time between admission and BSI among the cases was 15 days. Approximately one-third of patients who developed urinary tract-related BSI (32.2%) died while in the hospital, compared with 4.5% of the controls ($p < 0.001$).

The distributions of microorganisms identified in the cases and controls are illustrated in Table 2. *Enterococcus sp.* were the most common microorganisms isolated in both cases and controls, and were isolated more frequently in cases compared to controls ($p = 0.011$). Coagulase-positive staphylococcus was also isolated more frequently in cases ($p < 0.001$), while *Klebsiella sp.* were isolated more frequently among controls ($p = 0.04$).

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 compared to women ($p < 0.001$). Neutropenia, renal disease, and liver disease were among the strongest comorbid predictors of urinary tract-related BSI, increasing the odds approximately 11-fold ($p < 0.001$), 3-fold ($p < 0.001$), and more than 2-fold ($p = 0.003$), respectively (Table 3).

Although we did not detect a significant effect due to diabetes mellitus, we observed nearly a 5-fold increase in risk for urinary tract-related BSI among patients given insulin ($p < 0.001$). 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, $p = 0.89$).

We also detected a number of time-dependent treatment factors that may potentially 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 (i.e., *Enterococcus sp.*, *Candida sp.*, and *Escherichia coli*). The CART procedure revealed that the 6 best discriminators for urinary tract-related BSI were neutropenia, renal disease, inpatient insulin administration, urinary tract operation, 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 that 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 urinary tract operation (Terminal Node 4; 61.3% probability), and patients over 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 compared to 88 patients without BSI, the 80 patients with BSI were older and more frequently had an indwelling urethral catheter or obstructive urologic disease.⁵ Krieger and colleagues⁶ 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 identified male sex and infection with *Serratia marcescens* as risk factors for BSI. More recently, Saint and colleagues² conducted a case-control study identifying 95 cases with concordant positive blood and urine cultures > 48 hours after admission, matched with 142 controls with only positive urine cultures > 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 conferring increased risk in patients < 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 non-modifiable risk factor, this result supports previous findings^{2,6} and suggests that prevention 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 US, affecting over 25 million American 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 towards 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 for BSI.¹⁶ Using the administration of insulin (within 2 days prior of the index date) as a proxy for short-term hyperglycemia, the results from 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 of BSI, 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. Using a sensitive definition of severe neutropenia based on confirmed laboratory values, 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 a BSI. Other investigators have shown that as many as 30% of neutropenic patients develop BSI¹⁸ and may develop BSI an average of 2 days earlier than their non-neutropenic 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 and colleagues have described a similar increased risk of BSI among CKD patients not receiving hemodialysis.²¹ Although the mechanisms contributing to increased susceptibility to infection among CKD patients are not completely understood, it is possible that renal dysfunction is a marker for other conditions that increase host susceptibility.^{21,22} Alternately, it has been suggested that consequences of CKD (e.g., malnutrition, chronic inflammation, 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 non-parametric 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 one previous study² has examined how time-dependent medication use alters 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 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, while antibacterial use was associated with a reduced risk of BSI; these findings are consistent with 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 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 that developed urinary tract-related BSI in our hospital-based sample, as well as temporal changes in the microorganisms isolated in these nosocomial infections.³ Our investigation provides new evidence that *Enterococcus sp.* 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 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 sub-groups. Considering time-dependent risk factors, including inpatient medications, may also help guide clinical decisions in reducing this critical and costly patient safety problem.

Acknowledgments

Financial support. This project was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (R21 grant DK078717 to S.S.). Other than initial scientific review and approval for funding, the National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Klevens RM, Edwards JR, Andrus ML, Peterson KD, Dudeck MA, Horan TC. Dialysis Surveillance Report: National Healthcare Safety Network (NHSN)-data summary for 2006. *Semin Dial.* 2008; 21(1):24–28. [PubMed: 18251954]
2. Saint S, Kaufman SR, Rogers MA, Baker PD, Boyko EJ, Lipsky BA. Risk factors for nosocomial urinary tract-related bacteremia: a case-control study. *Am J Infect Control.* 2006; 34(7):401–407. [PubMed: 16945684]
3. Chang R, Greene MT, Chenoweth CE, et al. Epidemiology of hospital-acquired urinary tract-related bloodstream infection at a university hospital. *Infect Control Hosp Epidemiol.* 2011; 32(11):1127–1129. [PubMed: 22011543]
4. Saint S, Meddings JA, Calfee D, Kowalski CP, Krein SL. Catheter-associated urinary tract infection and the Medicare rule changes. *Ann Intern Med.* 2009; 150(12):877–884. [PubMed: 19528567]
5. Jerkeman M, Braconier JH. Bacteremic and non-bacteremic febrile urinary tract infection--a review of 168 hospital-treated patients. *Infection.* 1992; 20(3):143–145. [PubMed: 1644489]

6. Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. *J Infect Dis.* 1983; 148(1):57–62. [PubMed: 6350488]
7. Bahagon Y, Raveh D, Schlesinger Y, Rudensky B, Yinnon AM. Prevalence and predictive features of bacteremic urinary tract infection in emergency department patients. *Eur J Clin Microbiol Infect Dis.* 2007; 26(5):349–352. [PubMed: 17431694]
8. Leibovici L, Greenshtain S, Cohen O, Wysenbeek AJ. Toward improved empiric management of moderate to severe urinary tract infections. *Arch Intern Med.* 1992; 152(12):2481–2486. [PubMed: 1456860]
9. Rothman, KJ.; Greenland, S.; Lash, TL. *Modern epidemiology.* Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
10. Breiman, L. *Classification and regression trees.* Belmont, Calif: Wadsworth International Group; 1984.
11. Vanhorebeek I, Langouche L, Van den Berghe G. Tight blood glucose control with insulin in the ICU: facts and controversies. *Chest.* 2007; 132(1):268–278. [PubMed: 17625087]
12. Grey NJ, Perdriest GA. Reduction of nosocomial infections in the surgical intensive-care unit by strict glycemic control. *Endocr Pract.* 2004; 10 (Suppl 2):46–52. [PubMed: 15251640]
13. Griebing, TL. Urinary Tract Infection in Women. In: Litwin, MS.; Saigal, CS., editors. *Urologic diseases in America.* Washington, DC: National Institute of Diabetes and Digestive and Kidney Diseases; 2007.
14. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
15. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *N Engl J Med.* 1999; 341(25):1906–1912. [PubMed: 10601511]
16. Jeon, C. Increase in glucose levels in inpatients may indicate bloodstream infections. 51st International Conference on Antimicrobial Agents and Chemotherapy; Sept. 17–20, 2011; Chicago, IL.
17. Urabe A. Clinical features of the neutropenic host: definitions and initial evaluation. *Clinical infectious diseases.* 2004; 39(Supplement 1):S53. [PubMed: 15250022]
18. Feld R. Bloodstream infections in cancer patients with febrile neutropenia. *Int J Antimicrob Agents.* 2008; 32 (Suppl 1):S30–33. [PubMed: 18778919]
19. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin Infect Dis.* 1999; 29(2):239–244. [PubMed: 10476719]
20. Nassar GM, Ayus JC. Infectious complications of the hemodialysis access. *Kidney Int.* 2001; 60(1):1–13. [PubMed: 11422731]
21. James MT, Laupland KB, Tonelli M, Manns BJ, Culleton BF, Hemmelgarn BR. Risk of bloodstream infection in patients with chronic kidney disease not treated with dialysis. *Arch Intern Med.* 2008; 168(21):2333–2339. [PubMed: 19029498]
22. Dalrymple LS, Go AS. Epidemiology of acute infections among patients with chronic kidney disease. *Clin J Am Soc Nephrol.* 2008; 3(5):1487–1493. [PubMed: 18650409]
23. Foley RN. Infections in patients with chronic kidney disease. *Infect Dis Clin North Am.* 2007; 21(3):659–672. viii. [PubMed: 17826617]
24. Bittencourt PL, de Carvalho GC, de Andrade Regis C, et al. Causes of renal failure in patients with decompensated cirrhosis and its impact in hospital mortality. *Ann Hepatol.* 2012; 11(1):90–95. [PubMed: 22166566]
25. Almog Y. Statins, inflammation, and sepsis: hypothesis. *Chest.* 2003; 124(2):740–743. [PubMed: 12907568]
26. McGown CC, Brookes ZL. Beneficial effects of statins on the microcirculation during sepsis: the role of nitric oxide. *Br J Anaesth.* 2007; 98(2):163–175. [PubMed: 17251210]
27. Mekontso-Dessap A, Brun-Buisson C. Statins: the next step in adjuvant therapy for sepsis? *Intensive Care Med.* 2006; 32(1):11–14. [PubMed: 16283158]

28. Merx MW, Liehn EA, Janssens U, et al. HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. *Circulation*. 2004; 109(21):2560–2565. [PubMed: 15123521]
29. Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG. Statins: panacea for sepsis? *Lancet Infect Dis*. 2006; 6(4):242–248. [PubMed: 16554249]

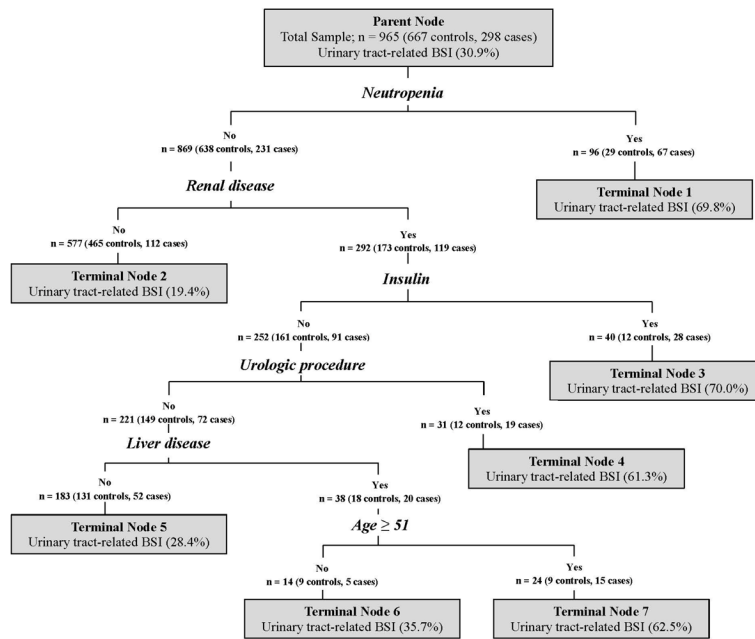


Figure 1.
High-Risk Patient Subgroups Identified by Classification and Regression Tree Analysis

Table 1

Descriptive Characteristics of Cases and Controls, 2000–2008

Characteristic	Cases n=298	Controls n=667	p-value
Age, mean (SD)	58.1 (15.3)	61.3 (14.9)	0.003
Length of stay, mean (SD)	41.3 (35.7)	26.2 (21.6)	<0.001
Male	164 (55%)	252 (38%)	<0.001
Cigarette use	140 (47%)	292 (44%)	0.393
Diabetes	69 (23%)	164 (25%)	0.690
Hypertension	130 (44%)	349 (52%)	0.015
Renal disease	153 (51%)	178 (27%)	<0.001
Liver disease	52 (17%)	46 (7%)	<0.001
Malignancy	121 (41%)	165 (25%)	<0.001
Urologic procedure	37 (12%)	30 (5%)	<0.001
Neutropenia	67 (22%)	29 (4%)	<0.001
Immunosuppressive therapy	136 (46%)	145 (22%)	<0.001
Antibacterial therapy	158 (53%)	382 (57%)	0.247
Insulin	33 (11%)	25 (4%)	<0.001

Results displayed for pharmacologic therapies were therapies that were administered during the hospital stay 2 days prior to the index date. Index date = bloodstream infection date of the case within each matched case-control set.

Table 2

Distribution of Microorganisms among Cases and Controls, 2000–2008

Microorganism (genus)	Cases (n=298)	Controls (n=667)	p-value
<i>Enterococcus sp.</i>	90 (30.2%)	149 (22.3%)	0.011
<i>Candida sp.</i>	50 (16.8%)	146 (21.9%)	0.082
<i>Escherichia coli</i>	41 (13.8%)	123 (18.4%)	0.090
Coagulase-positive staphylococcus	27 (9.1%)	17 (2.6%)	<0.001
<i>Pseudomonas sp.</i>	23 (7.7%)	48 (7.2%)	0.878
Coagulase-negative staphylococcus	17 (5.7%)	27 (4.1%)	0.331
<i>Klebsiella sp.</i>	17 (5.7%)	67 (10.0%)	0.037
<i>Enterobacter sp.</i>	14 (4.7%)	30 (4.5%)	1.000
<i>Proteus sp.</i>	5 (1.7%)	17 (2.6%)	0.546
<i>Citrobacter sp.</i>	4 (1.3%)	5 (0.8%)	0.601
<i>Acinetobacter sp.</i>	3 (1.0%)	2 (0.3%)	0.353
<i>Streptococcus sp.</i>	3 (1.0%)	11 (1.6%)	0.631
Other	4 (1.3%)	21 (3.1%)	0.158
Unspecified	-	4 (0.6%)	-

Other microorganism category includes *Elizabethkingae*, *Morganella*, and *Serratia* microorganisms

Table 3

Significant Predictors of Nosocomial Urinary Tract-Related Bloodstream Infection

Predictor variable	Odds Ratio *	95% Confidence Interval
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

* ORs presented above are from a multivariable conditional logistic regression analysis and were adjusted for all other covariates presented as well as: age, diabetes mellitus, ever vs. never cigarette smoking, hypertension, ICU status 2 days prior to 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. Index date = bloodstream infection date of the case within each matched case-control set.