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Risk Factors for Nosocomial Bacteremia Secondary to Urinary Catheter-Associated Bacteriuria: A Systematic Review

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Abstract

A systematic appraisal of evidence suggests that male patients in hospital may be at higher risk for bacteremia following urinary catheter-associated bacteriuria than females. Other risk factors include immunosuppressant medication, red blood cell transfusion, neutropenia, malignancy, and liver disease.

Keywords

Urosepsis; bacteremia; urinary catheter; risk factors; bacteriuria; infection control

Each year, more than 13,000 deaths are attributed to health care-associated urinary tract infections (Klevens et al., 2007). The vast majority of these infections are associated with urinary catheters (Hooton et al., 2010). Bacteriuria is a growth of bacteria in the urine and diagnosed by urine culture. Adult patients with urinary catheters develop bacteriuria at a rate of 8% per day during the first week (Garibaldi, Burke, Dickman, & Smith, 1974). One in 27 hospital patients with catheter-associated bacteriuria (CAB) goes on to develop secondary bacteremia (Saint, 2000) with a seven-day mortality of more than 30% (Melzer & Welch, 2013) and an attributable mortality rate of 12.7% (Bryan & Reynolds, 1984). The cost of bacteremia due to CAB was conservatively estimated at $2,836 per episode in 2000 (Saint, 2000) or approximately $3790 today (Friedman, 2014). The precise link between CAB and bacteremia remains unknown.

Identifying patients with CAB who are likely to progress to bacteremia would enable clinicians to direct interventions, such as early catheter removal, in-out catheterization, or use of condom catheters instead of indwelling urethral catheters to patients at highest risk for the most serious sequelae of CAB (Hooton et al., 2010). We conducted a systematic review to identify risk factors for bacteremia secondary to CAB among adults in acute care settings.

Methods

The Centre for Reviews and Dissemination Guidance for Undertaking Reviews in Health Care was used to develop a review protocol (Centre for Reviews and Dissemination, 2009). Electronic searches of Medline, Scopus, the Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Outbreak Database were conducted with the assistance of a medical librarian. Search terms were ("urosepsis" or "bacteremia-urine" or "sepsis-urine" or "urinary tract infections-complications") or (["bacteremia" or "sepsis" or 'bloodstream infection"] and ["urinary tract" or "urinary tract infections" or "urinary catheters" or "urinary catheterization" or "bacteriuria" or 'pyuria"]). The search was limited to human studies in adults, published in English between 1983 and 2012, and was later updated through August 2014. The exact Medline search code is listed in Figure 1. Reference lists of included articles and pertinent reviews were hand searched. We chose to limit our search to the past 30 years in order to be as comprehensive as possible, while ensuring that study findings would be relevant to today's highly complex clinical practice environment. A seminal guideline for the prevention of catheter-associated urinary tract infections was published in 1983 (Wong, 1983), and recommendations in subsequent guidelines have changed little over the intervening years (Conway & Larson, 2012). Therefore, clinical research into CAB from 1983 forward is likely applicable to current catheterized patient populations and settings.

We selected original, peer-reviewed research, including experimental, quasi-experimental, or observational studies; case series; and outbreak reports. We excluded grey literature, duplicate reports, reviews, single case reports, editorials, or commentaries. One researcher (LJC) initially screened all titles and abstracts, culling obviously irrelevant reports and erring on the side of over-inclusion. Then two researchers (EJC and LJC) independently screened titles and abstracts, and later, full texts. Exclusion criteria are listed in Figure 2. We excluded studies that sampled exclusively renal transplant or urology patients because these populations are known to be at higher risk for urosepsis than the general acute care population (Nicolle, 2013). We excluded studies where less than half of the patients with bacteriuria had urinary catheters, and no subgroup analysis was performed because our population of interest was patients with catheters. Factors unique to in dwelling catheters, such as bio film formation and constant but incomplete evacuation of urine from the bladder, may impact the risk for subsequent bacteremia.

The same two researchers independently extracted data from the included studies into a standard form. Data about study setting, design, sample, operational definitions, and analysis were extracted. Data about the study setting included author and affiliation, year published, country, city, institution, facility size and type, and types of units. Data about the study design included study aim, design, intervention (if any), data sources, and number of data reviewers. Data about the sample included method of recruitment and random assignment, inclusion and exclusion criteria, sample size and subgroup numbers, mean age and range, races, and disease states. Operational definitions included definitions of urinary tract infection or bacteriuria, bacteremia or sepsis, nosocomial, and health care-associated. Data about analysis included outcome variables and covariates, analytic approach, and significant and non-significant findings. Disagreements were resolved by consensus.

The quality of included observational studies was appraised using the Newcastle- Ottawa Scale (NOS) (Wells et al., n.d.). The NOS examines threats to validity common to observational studies, namely sampling bias, information bias, and confounding. It is composed of two checklists of nine items each – one for cohort studies and one for case-control studies. The NOS is recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Reeves, Deeks, Higgins, & Wells, 2011). The quality of experimental studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias, which assesses seven dimensions, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (Higgins, Altman, & Sterne, 2011). We chose these checklists because we wanted to focus on internal validity rather than on completeness of reporting or external validity, and we wanted to identify methodological strengths and weaknesses for our outcome of interest rather than assign a rating of overall quality. Two researchers (ELL and LJC) judged the risk of bias and resolved disagreements by consensus.

Results

The selection process is illustrated in Figure 2. Screening of 5,231 titles and abstracts and 79 full texts yielded 7 eligible studies (Arpi & Renneberg, 1984; Greene et al., 2012; Karchmer, Giannetta, Muto, Strain, & Farr, 2000; Khair et al., 2013; Krieger, Kaiser, & Wenzel, 1983; Leone et al., 2007; Rogers et al., 2011; Saint et al., 2006). Two articles that used the same sample and similar methodology to examine different risk factors are treated as one study for the purposes of this review (Greene et al., 2012; Rogers et al., 2011). Although both articles examined risk factors for bacteremia after CAB, one article specifically investigated blood transfusions, and the other explored multiple risk factors but not blood transfusions.

Characteristics of the three observational cohort (Arpi & Renneberg, 1984; Khair et al., 2013; Krieger et al., 1983), two case-control (Greene et al., 2012; Rogers et al., 2011; Saint et al., 2006), and two randomized controlled trials (RCTs) (Karchmer et al., 2000; Leone et al., 2007) are outlined in Table 1. For studies that conducted a subgroup analysis for bacteremia, only subgroup sample characteristics are listed. All studies were conducted in acute care hospitals in the United States or Europe. All studies used clinical and microbiology records as their primary sources of data.

The operational definitions of bacteriuria differed, ranging from 10^3 to 10^5 colony forming units per milliliter of single or multiple organisms. Five studies included all bacteria (Greene et al., 2012; Karchmer et al., 2000; Krieger et al., 1983; Leone et al., 2007; Rogers et al., 2011; Saint et al., 2006), one specifically included fungal pathogens, and two studies examined one genus (enterococci) (Khair et al., 2013) or species (*Staphylococcus aureus*) (Arpi & Renneberg, 1984). One study sampled patients with asymptomatic bacteriuria (Leone et al., 2007), and the remainder sampled bacteriuric patients with and without urinary tract symptoms. In two studies, 100% of patients had indwelling urinary catheters (Karchmer et al., 2000; Leone et al., 2007), and in three studies, the proportion of patients with catheters was between 57% and 86% (Arpi & Renneberg, 1984; Khair et al., 2013; Saint et al., 2006). In the two studies missing catheter data (Greene et al., 2012; Krieger et

al., 1983; Rogers et al., 2011), all bacteriurias were nosocomial, so it was assumed more than half of the patients had urinary catheters (Hooton et al., 2010). Five of the seven studies examined only nosocomial infections (Greene et al., 2012; Karchmer et al., 2000; Krieger et al., 1983; Leone et al., 2007; Rogers et al., 2011; Saint et al., 2006).

The mean or median age of participants was between 47 and 73 years, and the proportion of males varied from 37% to 95%. The outcome measure in one study was clinical sepsis (Leone et al., 2007); the remaining studies measured bacteremia. Secondary bacteremia was commonly defined as the same organism cultured in urine and blood; however, the amount of time between onset of bacteriuria and bacteremia differed between studies, as did the criteria for a matching organism. The rarity of bacteremia due to CAB is underlined in the small numbers of cases in the cohort studies and RCTs (range 6 to 33). The two case control studies identified 95 and 298 cases.

Quality Appraisal

All seven studies were at high risk of at least one type of bias. Tables 2 and 3 list the sources of bias by study design. We adapted the NOS for cohort studies by removing one question because the cohort studies in our review were simple observational studies (Arpi & Renneberg, 1984; Khair et al., 2013; Krieger et al., 1983), rather than the classic cohort design where subjects with a known exposure are compared to those not exposed. All three observational cohort studies used positive clinical cultures to define bacteremia, exposing them to ascertainment bias (bacteremia was demonstrated to be present but not absent) and detection bias (neutropenic patients may have had blood cultures drawn more frequently than other patients, biasing results in favor of finding high rates of bacteremia in neutropenic patients). In addition, none of the cohort studies used multivariable analysis to examine bacteremia outcomes, so results were likely confounded by measured and unmeasured factors.

In the two case-control studies, choice of control group created different biases. In one, controls were chosen from a subset of patients who had not had blood cultures drawn rather than from the same population as cases, creating a selection bias that may have exaggerated differences in risk factors (Saint et al., 2006). In the other, controls were chosen from the entire pool of patients; however, because clinical cultures were used to define bacteremia, patients who were bacteremic but who did not have blood cultures drawn (e.g., due to poor access, palliation, or subclinical symptoms) would have been misclassified as control patients (Greene et al., 2012; Rogers et al., 2011). In addition, these case-control studies were vulnerable to residual confounding (e.g., transfusions may be responsible for an association between malignancy and bacteremia), or confounding by indication (e.g., hyperglycemia, rather than insulin administration may be associated with bacteremia).

In one of the two RCTs, the impossibility of blinding clinicians to the intervention may have resulted in differences in care delivery that influenced the rates of bacteremia (Karchmer et al., 2000). In the other RCT, patients with recurrent positive urine cultures who may have been more likely to develop subsequent sepsis were excluded (Leone et al., 2007). Neither RCT was powered to find a difference in bacteremia or sepsis rates, creating a statistical bias toward the null for our outcome of interest.

Overall, the case-control studies were more aptly designed and conducted to answer our review question (Greene et al., 2012; Rogers et al., 2011; Saint et al., 2006). The strengths of the case control studies were adequate sample sizes, independent determination of exposures and outcomes by physician reviewers, consideration of multiple biologically plausible risks, assessment of potential interactions, and control for confounding by logistic regression.

Findings

Risks factors for bacteremia identified by the studies are summarized in Table 4. Male gender was identified as a risk factor in three of four studies (Greene et al., 2012; Krieger et al., 1983; Rogers et al., 2011; Saint et al., 2006). Men with CAB were found to have approximately twice the odds of developing bacteremia compared to females. This finding could have been confounded by the indication for catheterization in men (e.g., obstruction), which was not controlled for in any of the studies. Receipt of immunosuppressant medication was identified as an independent risk factor for bacteremia in both studies that examined it (Greene et al., 2012; Rogers et al., 2011; Saint et al., 2006); however, the studies reported very different odds ratios of 1.5 and 8, and when steroids were considered separately the direction of association was age-dependent. Receipt of antimicrobials was found to be protective in three of four studies (Arpi & Renneberg, 1984; Greene et al., 2012; Rogers et al., 2011; Saint et al., 2006), and the fourth study was likely underpowered to find a difference (Leone et al., 2007). Age, race, and service or ward were identified as non-significant factors by all studies that considered them.

Some risk factors were only explored in single studies. Transfusion of red blood cells was an independent risk; recipients had nearly five times the odds of bacteremia compared to non-recipients, and a dose-response was evident (Rogers et al., 2011). Neutropenia from any cause (Greene et al., 2012), liver disease (Greene et al., 2012), and malignancy (Saint et al., 2006) each independently increased the risk of developing bacteremia. Hypertension, human immunodeficiency virus infection, and receipt of statins were not significant predictors in multivariable analyses.

Several findings were contradictory. Urinary tract disease was found to increase risk of bacteremia nearly three-fold in one study (Greene et al., 2012), but was non-significant in three oth- ers (Arpi & Renneberg, 1984; Krieger et al., 1983; Saint et al., 2006). This may be because the definitions of urinary tract disease differed among the studies. Similarly, there was no agreement on the risk posed by urinary tract manipulation, defined variously as presence or type of catheter (Karchmer et al., 2000; Krieger et al., 1983), urological procedure (Greene et al., 2012), or surgery (Arpi & Renneberg, 1984). The urinary pathogen *Serratia marcescens* was more prevalent among patients who developed bacteremia compared to those who did not in an uncontrolled study (Krieger et al., 1983), but pathogen species was not a risk factor in a subsequent study using multivariable analysis (Saint et al., 2006), and vancomycin-resistance was not a significant risk factor for bacteremia in a study of enterococcal bacteriuria (Khair et al., 2013). Smoking was not associated with bacteremia in one case-control study (Greene et al., 2012), putting into question the weak association identified in an earlier case-control study (Saint et al., 2006). Finally, one study identified diabetes mellitus as a risk factor in patients less than 70 years of age (Saint et al., 2006),

whereas a subsequent study found that receipt of insulin was a risk factor independent of history of diabetes (Greene et al., 2012).

Discussion

Results of these studies suggest that males, patients who have received immunosuppressant medications or red blood cell transfusion, those not exposed to antimicrobials, and those with neutropenia, malignancy, or liver disease may be at increased risk for bacteremia secondary to CAB. However, the weight and quality of evidence supporting the identified risk factors are weak. Despite an exhaustive search encompassing more than 30 years, we found only seven pertinent studies, and no single factor was identified by more than one study as producing an odds ratio or relative risk greater than 2 or less than 0.5. It has been suggested that associations identified in observational studies should be considered weak unless the relative risk is greater than 2 or the odds ratio is greater than 3 (Grimes & Schulz, 2012). In addition, the findings were heterogeneous. This may be due in part to the lack of consistency in definitions of bacteremia, the wide variety of risk factors examined across studies, and the inclusion of patients with and without catheters in different proportions across studies. Although all studies were subject to some degree of bias, findings from the case-control studies are likely the most credible.

Few of the identified risk factors are modifiable. Red blood cell transfusions can and should be limited, but it is likely that the benefits of transfusion or of immunosuppressant medications will outweigh the risk of bacteremic CAB in many cases. Catheter use *is* modifiable; clinicians can limit the use of urinary catheters in patients at high risk for bacteremia. Clinicians can expect to receive regular, reliable feedback of local incidence rates of bacteremia due to CAB from their hospital's infection control department. Guidelines for the prevention of catheter-associated urinary tract infections recommend internal reporting of bacteremia attributable to CAB, as well as rates of symptomatic catheter-associated urinary tract infection and proportion of appropriate urinary catheter use (Gould et al., 2010; Lo et al., 2008). Since 2009, the Centers for Disease Control and Prevention (CDC) has included criteria for asymptomatic bacteremic CAB in its surveillance definitions for the National Healthcare Safety Network (NHSN) (CDC, 2014).

Hospitals must report these rates for adult and pediatric ICUs through NHSN, in order to fulfill the Centers for Medicare and Medicaid Service's Hospital In-patient Quality Reporting Requirements.

Future research into this question should focus on the role of diabetes and underlying urinary tract disease as risk factors, and should tease out the influence of urethral catheters independent of other urinary tract procedures or surgeries. Large case-control studies incorporating the risk factors identified in this review would help clarify the evidence base.

Findings of this review are supported by rigorous methods, including a medical librarian-assisted search, independent selection of studies by two reviewers using pre-determined inclusion criteria, and appraisal of potential for bias by two reviewers. In addition, our report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The

PRISMA Statement. However, our review has several limitations. First, we did not include grey literature, such as conference proceedings, because the reports may be preliminary or may not be peer-reviewed. This exclusion of unpublished studies may have resulted in an overestimation of risks because studies with significant results are more likely to be published (Song, Eastwood, Gilbody, Duley, & Sutton, 2000). Second, our inclusion of only English language studies may also have resulted in overestimation of risks because studies conducted in non-English-speaking countries are more likely to be published in an English-language journal rather than a native-language journal if the results are statistically significant (Egger et al., 1997). However, publication bias in this review is less likely given that most risk factor studies do not test an intervention and are therefore unlikely to generate a non-significant outcome that results in a decision not to publish. Third, our inclusion criteria were narrow, resulting in exclusion of many studies of risks for community-onset urosepsis, and more than 700 potential studies in renal transplant and urology patients. This weakened the weight and perhaps the quality of evidence, but strengthened the precision of our results. Fourth, our use of two different checklists to appraise potential for bias did not allow for a direct comparison of quality across all studies. However, the purpose of using the checklists was to help us identify bias within studies, rather than to rate and compare quality across studies. Finally, we were not able to conduct a meta-analysis or quantitative synthesis of any single risk factor because of the heterogeneity of outcome definitions and the variety of risk factors examined.

Conclusion

In conclusion, risk factors for bacteremia secondary to CAB have not been positively identified. However, weak evidence suggests that clinicians should be especially mindful of male patients who have received immunosuppressant medications or red blood cell transfusion, those not receiving antimicrobials, and those with neutropenia, malignancy, or liver disease. These patients should be targeted for daily monitoring and early removal of urinary catheters.

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Database(s): Ovid MEDLINE® 1946 to August Week 3 2014	
1.	Bacteremia.mp. or Bacteremia
2.	Sepsis.mp. or Sepsis
3.	Bloodstream infection.mp
4.	1 or 2 or 3
5.	Urinary tract infections or urinary catheterization or urinary tract or urinary catheters
6.	Bacteriuria
7.	Pyuria
8.	5 or 6 or 7
9.	4 and 8
10.	Urinary tract infections/co [complications]
11.	Urosepsis.mp.
12.	Bacteremia/ur [urine]
13.	Sepsis/ur [urine]
14.	9 or 10 or 11 or 12 or 13
15.	Limit 14 to (English language and humans and “year = 1983 – Current” and “all adult [19-plus years]”)

Figure 1.

Medline Search Strategy Code for Risk Factors for Nosocomial Bacteremia Secondary to Urinary Catheter-Associated Bacteriuria: A Systematic Review

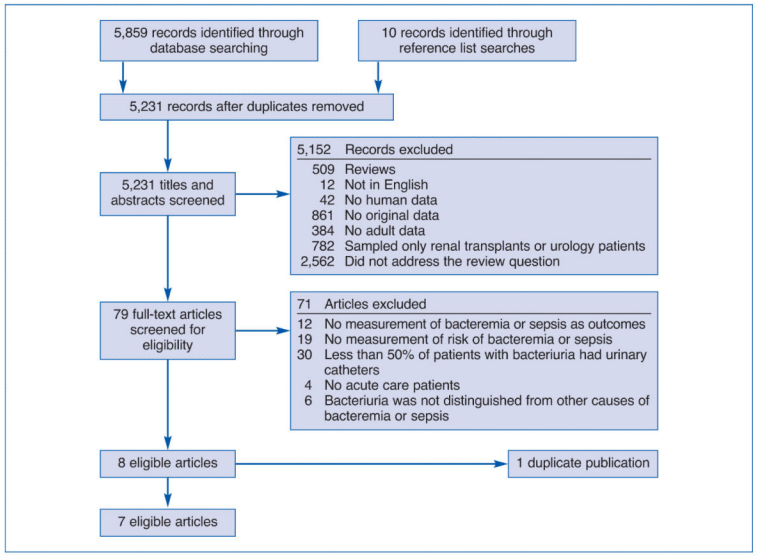

Figure 2.
Summary of Search and Screening Process

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Table 1

Characteristics of Included Studies in a Review of Risk Factors for Bacteremia Secondary to Catheter-Associated Bacteriuria

Author and Year Published	Design	Aim	Setting	Sample	Age Mean or Median (Range)	Male	Indwelling Urinary Catheter	Definition of Secondary Bacteremia or Sepsis
Krieger, Kaiser, & Wenzel (1983)	Prospective observational cohort	"To identify…particular organisms and patient characteristics which influence the probability of development of secondary bacteremias" (p. 57).	730-bed primary and tertiary care hospital in United States	Patients with nosocomial bacteriuria (≥ 10^5 cfu/mL or ≥ 10^4 cfu/mL in a symptomatic patient). *N* = 1,233	Missing	53%	Missing	Positive clinical blood culture with identical species and antibiogram to the urine organism, on the same day or subsequent to the bacteriuria, with no evidence of another primary site or mode of infection, and the patient's physicians prescribed antibiotic therapy. *N* = 33
Arpi & Renneberg (1984)	Retrospective observational cohort	"To describe the role of the urinary tract as the portal of entry for *Staphylococcus aureus* bacteremia and to define some useful risk factors" (p. 697).	920-bed community hospital in Denmark	Adult patients with *S. aureus* bacteriuria in pure culture (>10^5 cfu/mL), with or without symptoms of UTI. *N* = 132	73 (20 to 99)	81%	63%	Signs of generalized infection in combination with positive *S.aureus* blood culture with identical antibiogram and phage type to urine culture, greater than 48 hours after bacteriuria or UTI symptoms preceded simultaneous positive cultures by greater than 48 hours. *N* = 11
Khair et al. (2013)	Prospective observational cohort	"To describe the epidemiology of enterococcal bacteriuria in a hospital and compare the clinical picture and patient outcomes depending on vancomycin resistance" (p. 133).	1,250-bed tertiary care hospital in United States	Adult patients with enterococcal bacteriuria, including polymicrobial bacteriuria (≥ 5×10^4 cfu/mL, or 5×10^3 cfu/mL in patients with a catheter) with or without symptoms of UTI. *N* = 254	65 (17 to 96)	37%	57%	Definition missing. *N* = 8
Saint et al. (2006)	Matched case control	"Investigated the risk factors for developing bacteremia in patients with hospital-acquired bacteriuria" (p. 401).	Primary care and referral Veterans Affairs hospital in United States	Adult patients with nosocomial bacteriuria (≥ 10^3 cfu/mL of a single predominant bacterial or fungal species) with or without symptoms. *N* = 237	66 (26 to 98)	95%	86%	Blood culture obtained within 30 days of a urine culture that grew the same organism species. *N* = 95
Rogers et al. (2011) and Greene & Schulz (2012)	Matched case control	"To examine both previously identified and novel risk factors that may alter the risk of urinary tract related [bloodstream infection]" (p. 1002).	800-bed tertiary care referral hospital in United States	Adult patients with nosocomial bacteriuria (> 10^3 cfu/mL of a single organism) with or without symptoms of UTI. *N* = 965	60 (21 to missing)	43%	Missing	Positive clinical blood culture obtained on the same day or within 14 days after a clinical urine culture that grew the same organism. *N* = 298

Author and Year Published	Design	Aim	Setting	Sample	Age Mean or Median (Range)	Male	Indwelling Urinary Catheter	Definition of Secondary Bacteremia or Sepsis
Karchmer, Giannetta, Muto, Strain, & Farr (2000)	Cluster randomized crossover trial	"To assess the efficacy of a silver-alloy, hydrogel-coated latex urinary catheter for the prevention of nosocomial catheter-associated [urinary tract infections]" vs. a silicone-coated latex catheter (p. 3294).	600-bed primary and tertiary care hospital in United States	Patients on all wards except pediatrics, obstetrics, gynecology, or psychiatry, who required a urinary catheter. *N* = 27,878	Missing	Missing	100%	Infection preventionists used Centers for Disease Control and Prevention definitions. An organism isolated from blood culture is compatible with a related nosocomial catheter-associated symptomatic UTI or asymptomatic bacteriuria. *N* = 14
Leone et al. (2007)	2-arm randomized controlled trial	"Determining the effect on the occurrence of urosepsis of a treatment with a short course of antibiotics and indwelling urethral catheter replacement versus no antibiotic, no replacement" (p. 727).	Tertiary care hospital in France	Adult intensive care unit patients with nosocomial asymptomatic bacteriuria (≥ 10^5 cfu/mL of no more than 2 different species). *N* = 60	47 (range missing)	42%	100%	Sepsis related to positive urine cultures; with at least two of four signs: temperature greater than 38 degrees Celsius or less than 36 degrees Celsius; HR greater than 90 beats/minute; breathing rate greater than 20 cycles/minute or $PaCO_2$ less than 32 mmHg or mechanical ventilation; white blood cell count greater than 12 g/L or less than 4 g/L. *N* = 6

Notes: UTI = urinary tract infection, cfu/mL = colony forming units per milliliter, $PaCO_2$ = partial pressure carbon dioxide.

Table 2

Risks of Bias in Included Observational Cohort and Case-Control Studies

Cohort Studies	**Krieger, Kaiser, & Wenzel (1983)**	**Arpi & Renneberg (1984)**	**Khair et al. (2013)**
Was the observed cohort representative?	Yes	Yes	Yes
Were exposures/risk factors ascertained with minimal bias?	Yes	Yes	Yes
Was bacteremia or sepsis demonstrated to be absent at the start of the study?	No, clinical cultures were used	No, clinical cultures were used	No, clinical cultures were used
Did the study control for antimicrobial treatment of urinary tract infection?	No, not measured	No, only unadjusted analysis	No, only unadjusted analysis for bacteremia outcome
Did the study control for immuno-compromised status?	No, only bivariate analysis	No, only bivariate analysis	No, only bivariate analysis for the bacteremia outcome
Was bacteremia or sepsis ascertained with minimal bias?	Yes	Yes	Unclear whether sources of bacteremia other than UTI were ruled out
Was follow-up long enough for bacteremia or sepsis to occur (i.e., greater than 7 days or until discharge)?	Yes	Yes	Yes
Was missing patient data minimal, or is a description provided?	Unclear: no statement	Unclear: no statement	Unclear: no statement

Case-Control Studies	**Saint (2006)**	**Rogers et al. (2011) Greene et al. (2012)**	
Was the case definition of bacteremia or sepsis adequate?	Unclear whether sources of bacteremia other than UTI were ruled out	Yes	
Were the cases representative?	Yes	Yes	
Were controls derived from the same population as cases?	No, controls were chosen from only those patients who had no blood cultures drawn	Yes	
Was the control definition of no bacteremia/sepsis adequate?	Yes	No, controls included patients with negative blood cultures or no blood cultures	
Did the study control for antimicrobial treatment of urinary tract infection?	Yes	Yes	
Did the study control for immunocompromised status?	Yes	Yes	
Were exposures/risk factors ascertained with minimal bias?	Yes	Yes	
Was the same method of ascertainment of exposure/risk factors used for cases and controls?	Yes	Yes	
Was the non-response rate the same for cases and controls?	Yes	Unclear: no description	

Notes: Bias assessed using the Newcastle-Ottawa Scale (Wells et al., n.d.). UTI = urinary tract infection.

Table 3

Risks of Bias in Included Randomized Controlled Trials

	Karchmer, Giannetta, Muto, Strain, & Farr (2000)	**Leone et al. (2007)**
Random Sequence Generation	Low risk of bias. Sequence generation was not described, but the crossover design minimizes risk.	Low risk of bias.
Allocation concealment	Low risk of bias. Allocation concealment is not described, but the crossover design minimizes risk.	Unclear risk of bias. Allocation concealment was not described, and foreknowledge of allocation to the intervention could have resulted in sampling bias.
Blinding of participants and personnel	High risk of bias. The impossibility of blinding caregivers to the intervention may have resulted in differences in care delivery that influenced outcomes.	Low risk of bias. The impossibility of blinding was unlikely to influence care delivery because a strict care protocol was in place.
Blinding of outcome assessment	Low risk of bias. Although not blinded, trained infection preventionists applied standardized definitions to classify outcomes.	Low risk of bias. Although the data analyst was blinded, there was no mention of the investigators who classified outcomes being blinded. However, the physiologic criteria for sepsis were objective, as were the urine cultures.
Incomplete outcome data	Unclear risk of bias. One quarter of infections were in patients who received catheters different from that assigned to their ward, and the bacteremia outcome was analyzed at the ward level. Low risk of bias for other outcomes, which were analyzed based on actual catheter use.	Low risk of bias. The number and reason for pre-randomization exclusions were reported, and no attrition was reported; participants in the control group treated with antibiotics for urosepsis (n = 3) were not excluded from the analysis.
Selective reporting	Low risk of bias.	Low risk of bias.
Other sources of bias	High risk of statistical bias. Although the study was properly powered for the primary outcome, it was likely underpowered to find a difference in bacteremia rates.	High risk of sampling bias. “Patients were not included…if they had recurrent positive urine cultures after the study period” (p. 727). Thus, patients more likely to develop sepsis may have been systematically excluded. High risk of statistical bias. The study was likely underpowered to find a difference in the occurrence of urosepsis, its primary aim.

Note: Bias assessed using the Cochrane Collaboration Tool for Assessing Risk of Bias (Higgins et al., 2011).

Table 4

Risk Factors for Bacteremia Secondary to Urinary Catheter-Associated Bacteriuria Identified in Included Studies

	Unadjusted Analyses			Multivariable Analyses		Randomized Controlled Trials	
	Krieger, Kaiser, & Wenzel (1983)	**Arpi & Renneberg (1984)**	**Khair et al. (2013)**	**Saint et al. (2006)**	**Rogers et al. (2011) Greene et al. (2012)**	**Karchmer, Giannetta, Muto, Strain, & Farr (2000)**	**Leone et al. (2007)**
Male Gender	Males (3.7%) vs. females (1.6%) ($p < 0.05$)	NS		OR = 1.88 CI = 1.62 to 2.18	OR = 2.18 CI = 1.52 to 3.12		
Age	NS	NS		NS	NS		
Race	NS			NS			
Smoking				OR = 1.26 CI = 1.01 to 1.57	NS		
Co-morbidities	Nervous system or sensory organ disease (9.0%) protective vs. without disease (28.3%) ($p = 0.015$) Trauma NS Circulatory disease NS Congenital abnormality NS Endocrine disorder NS Immune deficiency NS Musculoskeletal disease NS Neoplastic disease NS Pregnancy NS General surgery NS	NS		Malignancy OR = 1.94 CI = 1.06-3.55 Diabetes mellitus Age younger than 70 years OR = 6.19 CI = 1.30 to 29.40 Diabetes is protective if age greater than or equal to 70 years OR = 0.11 CI = 0.02 to 0.83 HIV infection NS	Neutropenia OR = 10.99 CI = 5.78 to 20.88 Liver disease OR = 2.34 CI = 1.35 to 4.06 Diabetes mellitus NS Hypertension NS		
Urinary tract disease	Genitourinary tract disease NS	Obstruction NS		Renal insufficiency NS	Renal disease OR = 2.96 CI = 1.98 to 4.41		
Urinary tract manipulation	Manipulation including catheter (72.7%) protective vs. no manipulation (85.7%) ($p = 0.038$)	Instrumentation or surgery NS			Urological procedure OR = 2.49 CI = 1.31 to 4.73	Silver-coated catheter vs. uncoated NS RR = 0.56 CI = 0.19 to 1.66	
Antimicrobial		Appropriate (0%) protective vs. inappropriate or none (15.9%) ($p < 0.001$)		Protective OR = 0.76 CI = 0.68 to 0.85	Protective OR = 0.66 CI = 0.44 to 0.97		Three-day course antibiotic with catheter change vs. standard of care NS ($p = 1.0$)

	Unadjusted Analyses			Multivariable Analyses		Randomized Controlled Trials	
	Krieger, Kaiser, & Wenzel (1983)	**Arpi & Renneberg (1984)**	**Khair et al. (2013)**	**Saint et al. (2006)**	**Rogers et al. (2011) Greene et al. (2012)**	**Karchmer, Giannetta, Muto, Strain, & Farr (2000)**	**Leone et al. (2007)**
Urinary pathogen	*Serratia marcescens* vs. other pathogen ($p < 0.05$)		Vancomycin-resistant enterococcus (6%) vs. sensitive (2%) NS ($p = 0.1$)	Species NS			
Transfusion					Red blood cells OR = 4.84 CI = 2.90 to 8.06 Platelets, plasma NS		
Immuno-modulating drugs				Immunosuppressants OR = 8.13 CI = 1.02 to 64.83 Corticosteroids age younger than 70 years OR = 14.24 CI = 4.76 to 42.63	Immunosuppressants OR = 1.53 CI = 1.04 to 2.25 Insulin OR= 4.82 CI = 2.52 to 9.21 Statins NS		
Immuno-modulating drugs				Corticosteroids are protective if age greater than or equal to 70 years OR = 0.08 CI = 0.02 to 0.34			
Service or ward	Surgery vs. medicine vs. other NS			Ward vs. ICU vs. nursing home unit vs. spinal cord unit NS	ICU vs. non-ICU NS		
Length of stay before bacteriuria				CI 1.01-1.04 7/9			
Quality score*	4/8	4/8	3/8		7/9	**4/7**	5/7

*Higher score = lower risk of bias; bias assessed using the Newcastle-Ottawa Scale (Wells et al., n.d.) or the Cochrane Collaboration Tool for Assessing Risk of Bias (Higgins et al., 2011) for experimental studies.

Notes: NS = no significant difference found, OR = odds ratio, CI = 95% confidence interval, ICU = intensive care unit, RR = relative risk.