The Role of Urinary Catheters in Development of Nosocomial Urinary Tract-Related Bacteremia

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Abstract

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This dissertation examines risk factors for bacteremia secondary to catheter-associated bacteriuria (CAB), specifically the potential risk of continued catheter presence, and assesses the degree to which hospitals in the United States (US) have implemented strategies to reduce unnecessary use of urinary catheters. In Chapter One, the problems of urinary tract-related bacteremia and unnecessary use of urinary catheters are introduced and their significance is described. In Chapter Two, a systematic review of the literature identifying risk factors for bacteremia secondary to CAB among adults in acute care settings is reported. In Chapter Three, a case control study elucidating risk factors for secondary bacteremia among adult patients with nosocomial CAB is reported, including an assessment of the risk posed by the continued presence of a urinary catheter after the onset of CAB. In Chapter Four, the prevalence and predictors of urinary catheter reduction policies in US hospitals is reported. In Chapter Five, findings of the three studies are summarized and overarching conclusions are provided including strengths, limitations, and implications for research, practice, and policy.

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Chapter One: Introduction

In this chapter I introduce two related problems; urinary tract-related bacteremia and unnecessary use of urinary catheters. First, I describe the epidemiology of the problems. Second, I explain the significance of research into these problems, listing the potential utility of research findings for health care providers in general and nurses in particular. Third, I identify gaps in the literature addressing these problems. Fourth, I state the aims of my dissertation and outline how it is organized. Finally, I give a brief explanation of the conceptual frameworks underpinning my work.

Problems

Urinary Tract Infections

Healthcare-associated infections (HAI) are common, costly, and largely preventable complications of hospital care. One in 25 hospitalized patients in the United States (US) has an HAI, and the estimated incidence is more than 700,000 HAI per year.[1] Urinary tract infection is one of the most common HAI, and more than 70% are associated with urinary catheter use.[2] Catheter-associated urinary tract infections (CAUTI) are the most frequently occurring device-associated infection in hospitals.[1]

The incidence of CAUTI ranges from 1.2 to 5.0 per 1,000 catheter days in intensive care units (ICUs) and 0.4 to 5.3 per 1,000 catheter days in adult wards in the US, with higher rates seen internationally.[3,4] More than 36,000 CAUTI were reported to the National Healthcare Safety Network (NHSN) for 2012.[3] Since reporting of CAUTI in non-ICU areas via NHSN was voluntary at that time, the actual incidence of CAUTI is likely much higher.

In this dissertation, use of the term CAUTI is restricted to symptomatic infections, where bacteriuria is associated with fever or localized urinary tract symptoms. The broader term

catheter-associated bacteriuria (CAB) is used when no distinction is made between asymptomatic and symptomatic infection, such as in many research studies. CAB costs the healthcare system $900 per episode, resulting in 30 million dollars of unnecessary expense annually.[5] Moreover, patients with CAB constitute a large reservoir of antimicrobial-resistant organisms, creating a risk for cross-infection.[6-8] Most importantly, CAB puts patients at risk for secondary bacteremia.

Secondary Bacteremia

In prospective studies, the incidence of patients developing bacteremia after CAB ranges from 0.4% to 4%.[9,10] Bacteremia secondary to a urinary source comprises 21% of all nosocomial bacteremias.[11] In the latest estimate available from 2000, the cost of bacteremic CAB was conservatively estimated at $2800.[10] It is difficult to determine related mortality; however, in one prospective study conducted from 1977 to 1981, overall mortality for patients with nosocomial urinary tract-related bacteremia was 30.8% and the directly attributable mortality was 12.7%.[12] Improvements in sepsis care since that time may have lowered mortality rates, despite increasing patient acuity during the same period. In a recent Canadian study of 1,510 episodes of nosocomial urinary source bacteremia, 60% of which were associated with a urinary catheter, the 30 day all-cause mortality was 15%.[11] In the most recent US national estimates available, CAB and secondary bacteremia caused or contributed to more than 13,000 deaths per year.[13]

Urinary Catheters

Fortunately, CAB and its serious sequelae are highly preventable. Between 65 and 70% may be prevented by implementing evidence-based strategies.[14] Strategies recommended in practice guidelines have been remarkably consistent from 1980 to the present, focusing on one overriding principle – minimize unnecessary urinary catheter use.[15] Toward this end, experts

recommend substituting intermittent catheterization or condom drainage for indwelling catheters, using bladder ultrasound scanners to identify or rule out urinary retention, using electronic, paper, or verbal reminders that a catheter is in place, and using automatic stop orders or nurse-driven protocols to ensure catheters are discontinued as soon as they are no longer needed.[16-20] These strategies are based on the premise that catheters are frequently inserted without appropriate indications, or are forgotten once they are inserted.[21]

Approximately 31% of patients in hospital has a urinary catheter in place.[22] Catheter utilization ratios are highest in adult ICUs, ranging from 50% in cardiac and burn ICUs to 78% in trauma ICUs.[3] Most ICU patients legitimately require a catheter because of the need for hourly monitoring of urinary output. Five other appropriate indications for catheter use, according to guidelines promulgated by the Centers for Disease Control and Prevention (CDC) are acute urinary retention or obstruction, select surgical procedures, sacral or perineal wound healing in incontinent patients, patient comfort at the end of life, or prolonged immobilization.[19] Despite these specific guidelines, studies have shown that outside the ICU, 30 to 40% of catheters are inserted without an appropriate indication.[22] In fact, in a survey of US hospitals, more than one third reported that they placed catheters for reasons such as urinary incontinence without obstruction or patient/family request, indications which would be considered inappropriate by CDC.[23]

Codifying appropriate indications for catheterization in hospital-wide policies is an important initial step in minimizing unnecessary catheter use, with the ultimate goal of reducing CAUTI.[24] An association between catheter reduction and CAUTI reduction has been demonstrated. A recent national study found that compared to other states, the reduction in CAUTI rates from 2009 to 2010 was greater in Michigan, where a significantly larger proportion

of hospitals routinely monitored catheter use, and routinely used bladder ultrasound, catheter reminders, stop orders, and nurse-initiated discontinuation protocols.[25] In addition, a meta-analysis of interventional studies showed that catheter reminder systems and automatic stop orders decrease rates of CAUTI by half.[26]

In summary, bacteremia secondary to CAB endangers individual patients and incurs high costs for the health care system. Careful attention to catheter use could reduce the incidence of CAB, and with it secondary bacteremia. Elucidating risk factors for bacteremia secondary to CAB, and examining what is being done by US hospitals to reduce unnecessary catheter use would contribute significantly to clinical practice and research.

Significance

Identifying Risks for Bacteremia

Identifying risk factors for bacteremia secondary to CAB would help nurses target high risk patients for daily monitoring of catheter presence, physician reminders, and early removal. If after careful assessment a urinary catheter is still indicated, potential alternatives could be considered such as intermittent catheterization or use of a condom catheter for males. Developing a profile for patients at high risk for secondary bacteremia could also aid in the development of nurse-driven protocols for catheter removal. Written order sets that specify conditions under which a nurse may remove a catheter without prior physician approval could incorporate criteria that are derived from knowledge of risks.

Conversely, identifying patients at low risk for secondary bacteremia could reduce inappropriate antimicrobial prescribing. Half of all patients in acute care hospitals receive antimicrobials, and the urinary tract is the second most common site of infection treated.[27] Most CAB are asymptomatic;[9] and with few exceptions, antimicrobial treatment is not recommended

for patients with CAB who are asymptomatic.[28] Yet one to two-thirds of asymptomatic CAB are treated.[29-32] Unnecessary treatment can result in avoidable side effects or toxicity, allergic reaction, diarrhea and *Clostridium difficile* disease, and emergence of resistant organisms.[33-35] In addition, inappropriate treatment wastes money. Characterizing patients at low risk for bacteremia would provide clinicians with further reason to refrain from treating asymptomatic CAB. In cases where the evidence for or against treatment of asymptomatic CAB is inconclusive, such as for surgical patients at the time of catheter removal to prevent development of symptomatic infection, a risk profile would also aid clinical judgment.[36]

Measuring Adoption of Catheter Use Policies

Measuring the extent to which urinary catheter guidelines are being implemented in US hospitals would provide a basis for regional implementation collaboratives. Efforts and resources could be directed toward areas where uptake is slow. Also, a report of proportions of hospitals that have adopted strategies to limit catheter use could serve as a wake-up call to encourage lagging hospitals to adopt proven strategies. In addition, an assessment of organizational factors that predict policy adoption could inform future implementation research regarding what factors encourage or deter hospitals from adopting evidence-based policies for HAI prevention.

Importance to Nursing

These issues are highly relevant to nursing practice and research. Nurses insert and maintain catheters, and monitor patients for complications such as CAUTI and secondary bacteremia. Nurses influence physicians' decisions to use or remove catheters, and nurses participate in developing catheter use policies for health care systems.[37] Thus, catheters and CAUTI are nursing concerns. CAUTI are *nursing-sensitive outcomes*; that is, they have been shown to be associated with the quantity and quality of nursing care, and they are thought to be

more highly related to nursing care than to medical care or institutional characteristics.[38] CAUTI are endorsed as nursing-sensitive outcomes by the National Quality Forum[39,40] and are included in the National Database of Nursing Quality Indicators developed by the American Nurses' Association.[38] Evidence of risk factors for bacteremia secondary to CAB, and of what is being done by US hospitals to limit catheter use would support the broad mission of the National Institute of Nursing Research to prevent disease and build the scientific basis for clinical practice.[41] Results could serve as a basis for future interventional studies of specific risk-reduction strategies.

Gaps in the Literature

Identifying Risks for Bacteremia

Prior to beginning this dissertation, we conducted a preliminary survey of the literature for studies of risk factors for bacteremic urinary tract infection and found only five reports.[42-46] All of the studies included patients with and without indwelling catheters, and most identified urethral catheterization as a significant risk factor for secondary bacteremia.[43,45] Independent predictors of bacteremia identified in at least one multivariate analysis include male gender,[44] cigarette use,[44] malignancy,[44] diabetes mellitus,[44] red blood cell transfusion,[46] and receipt of immunosuppressants,[44] corticosteroids,[44] or antimicrobials.[44] Findings varied greatly among the studies and were sometimes contradictory. For example, older age was found to be a risk factor in one study,[43] protective in another,[46] a modifier in another,[44] and non-significant in two others.[42,45]

Methodological problems were abundant in these observational studies, greatly impeding the utility of the findings. Potential confounding was a common problem. Two studies did not employ multivariate analytic techniques, thus, important concurrent risk factors may have

confounded results.[42,43] Two studies that utilized inpatient chart review did not control for time at risk.[43,45] Duration of catheterization was not measured in any of the studies and only one study examined risk factors arising during the interval between onset of urinary tract infection and bacteremia.[46] Thus, no information was available regarding the potential impact of continued catheter presence after bacteriuria on the subsequent development of bacteremia. The studies examined a heterogeneous group of underlying illnesses, and none employed an aggregate measure of comorbidity such as the Charlson Comorbidity Index.[47] Most of the studies were limited by small sample sizes in single hospitals. Two studies had limited external validity in that they sampled patients presenting with symptomatic urinary tract infection for outpatient consultation or emergency care, making it difficult to apply the findings to hospitalized patients with catheters.[43,45] In one well-designed study that would otherwise be highly generalizable to hospital patients with CAB, the sample was comprised of 95% males.[44]

Based on this initial survey of the literature, two things were apparent. First, a systematic review of risk factors for bacteremia secondary to CAB was needed in order to capture more studies applicable to inpatient populations, to formally appraise the potential for bias within studies, and to generate a profile of modifiable and non-modifiable risk factors. Second, additional research was needed into risk factors for bacteremia secondary to CAB.

Measuring Adoption of Catheter Use Policies

A single study of the prevalence and predictors of catheter use policies in US hospitals was reported prior to this dissertation work. In 2005, Saint and colleagues surveyed a random sample of non-federal acute care hospitals and Veterans Affairs (VA) hospitals in the US concerning urinary tract infection prevention practices.[48,49] Only 44% of participating hospitals monitored which patients had urinary catheters in place and 26% monitored duration of

catheterization. No single catheter reduction strategy was widely used. A small proportion of hospitals reported regularly using portable bladder ultrasound (30%), condom catheters (14%), suprapubic catheters (9%), or catheter reminders or stop-orders (9%). Nearly one third of hospitals did not monitor CAUTI rates. The survey was well-designed, used a national random sample of hospitals stratified by size, and the response rate was high (72%). However, the survey did not query whether participating hospitals had codified catheter reduction practices into policy, nor did it assess a possible relationship between catheter reduction strategies and CAUTI rates. Also, the survey was conducted before the Centers for Medicare & Medicaid Services announced plans to stop reimbursing hospitals for charges associated with nosocomial CAUTI. From this initial survey of the literature, we concluded that because of the paucity of evidence and the changes in reimbursement policy, further research was needed to assess the extent to which US hospitals were implementing catheter reduction strategies.

In summary, although unnecessary catheter use and bacteremia secondary to CAB are significant problems with great importance to nurses, little research has addressed risk factors for secondary bacteremia or implementation of catheter reduction strategies. Thus, the purpose of this dissertation is to examine risk factors for bacteremia secondary to CAB, specifically the potential risk of continued catheter presence, and to assess the degree to which US hospitals have implemented strategies to reduce unnecessary use of urinary catheters. Our aims are as follows:

Aims

1. Identify risk factors for bacteremia secondary to CAB among adults in acute care settings. To answer this aim, we conducted a systematic review of the literature.

2. Describe risk factors for secondary bacteremia among adult patients with nosocomial CAB and determine whether or not continued catheter presence increases the risk for subsequent bacteremia. To answer this aim, we conducted a case control study.
3. Describe the presence of and adherence to catheter reduction policies in US hospitals, and identify predictors of policy adoption. To answer this aim, we analyzed responses to a national survey.

Organization

The three aims were addressed in three separate studies, each of which has been published or is prepared for publication according to the specific requirements and limitations of the intended journal. Reports of the three studies comprise the chapters immediately following this introduction. The first manuscript (Chapter Two: Risk Factors for Nosocomial Bacteremia Secondary to Urinary Catheter-Associated Bacteriuria: A Systematic Review) is accepted for publication in the journal *Urologic Nursing*. The second manuscript (Chapter Three: Risk Factors for Secondary Bacteremia in Patients with Catheter-Associated Bacteriuria: A Case-Control Study) is planned for submission to the *American Journal of Critical Care* after comment by dissertation committee members. The third paper (Chapter Four: Adoption of Policies to Prevent Catheter-Associated Urinary Tract Infections in US Intensive Care Units) was published in the *American Journal of Infection Control*.[50] Chapter Five summarizes the findings from the studies and provides overarching conclusions.

The methods for each study, including the data sources and variables, are described within each manuscript. The conceptual frameworks underlying the case-control study and the survey are not included in the manuscripts; therefore, they are described below. No specific theoretical framework was used to guide the systematic review.

Conceptual Frameworks

Aims 2 and 3 were addressed using two different theoretical frameworks.

Epidemiologic Triad

Aim 2, to describe risk factors for secondary bacteremia among adult patients with nosocomial CAB using a case control study, was addressed using the classic epidemiologic triad of agent, host, and environment, as adapted in **Figure 1.1**. Risk factors for bacteremia identified in our initial survey of the literature were placed within one of the three categories, along with risks which we considered plausible but which had not yet been studied, such as duration of catheterization after CAB. We conceptualized the healthcare environment broadly as including medical care and the physical environment. According to the model, acting on any of the risks may prevent bacteremia.[51]

The framework is a well-established epidemiologic model that has served as the basis for conceptualizing infectious diseases, chronic diseases, and injury.[51,52] It may be used to test hypotheses or simply to describe associations. It is particularly useful for researching multifaceted problems, where the etiology may be separated from the outcome by a long latency, multiple modifiers, or requisite interactions, and where the micro and macro-environments are thought to influence the outcome.[51,52] Thus, it is well-suited to guide this investigation into the complex interplay of factors associated with bacteremic CAB. Epidemiologic models have been criticized for seeking to demonstrate relationships between diseases and persons, places, or events, without postulating specific biologic mechanisms for the relationships (so-called "black box" theories).[52,53] Supporters of epidemiologic models argue that such circumstantial evidence can be helpful in preventing and controlling illness, even when exact causation is unknown.[53]

Such evidence can generate theory and can guide future experimental research into the causal pathway from CAB to bacteremia.

Donabedian's Model

Aim 3, to describe the presence of and adherence to catheter reduction policies in US hospitals, and to identify predictors of policy adoption, was addressed using data from a survey conducted prior to this dissertation work.[54] The survey, designed by a team of researchers not including myself, was based on Donabedian's model for assessing the quality of healthcare.[55]

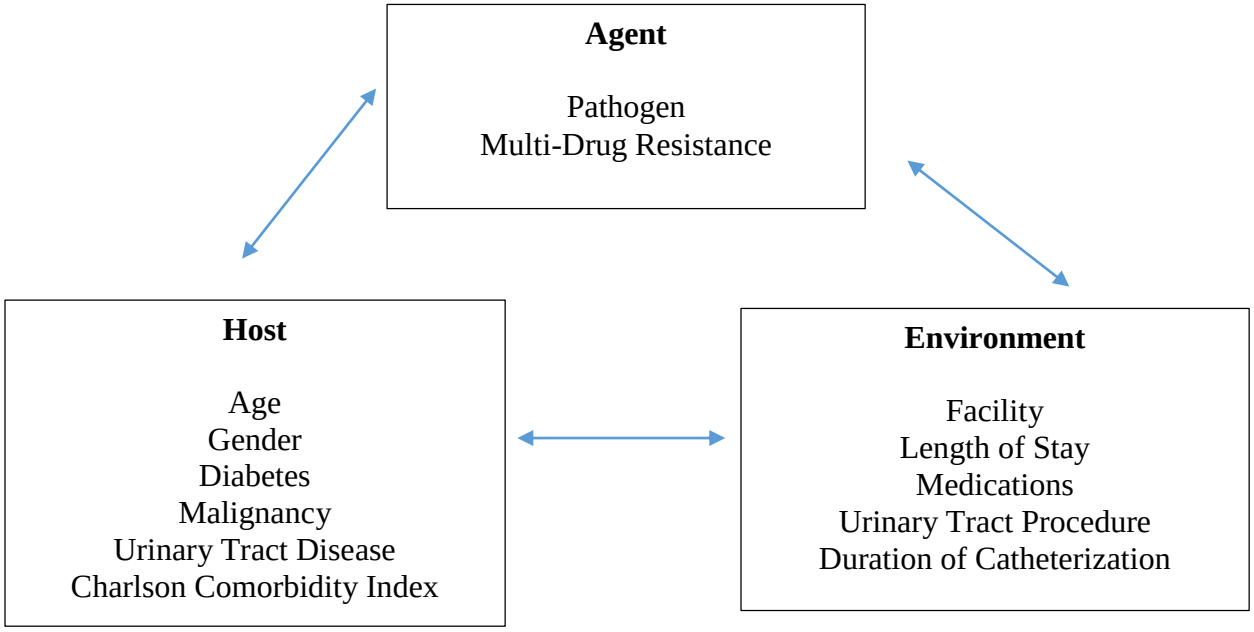
Donabedian proposed that the quality of medical care could be judged by examining a combination of factors; namely, the structures, processes, and outcomes of care.[55] Health outcomes and the processes of care can be intuited; however, what is meant by the structures of care warrants clarification. The structures of care include "the material and social instrumentalities that are used to provide care. These include the number, mix, and qualifications of the staff; the manner in which the staff is organized and governed; space, equipment, and other physical facilities; and so on."[56 [p.857]] Factors assessed in the survey were based on existing literature, and their classification as a structure, process, or outcome are shown in **Figure 1.2**.

Donabedian recognized that attempts to measure health care quality are fraught with difficulties, perhaps most importantly an inability to account for the uniqueness of each patient and the resultant complexities facing providers as they tailor care for individual patients.[56] One approach that attempts to take this complexity into consideration is to measure whether or not a minimum standard of care for all patients has been met, rather than measuring the quality of care on a continuum from poor to excellent. For this reason, our process measures were based on longstanding, widely-disseminated guideline recommendations for reducing unnecessary catheter use. Donabedian specified two caveats; (1) the interdependent influences of structures and

processes on outcomes must be assessed, and (2) the characteristics of the patient populations should be controlled for when making comparisons of quality.[56] For this reason, we employed a multivariable analysis of structural factors and processes while controlling for hospital characteristics that reflected the patient populations served.

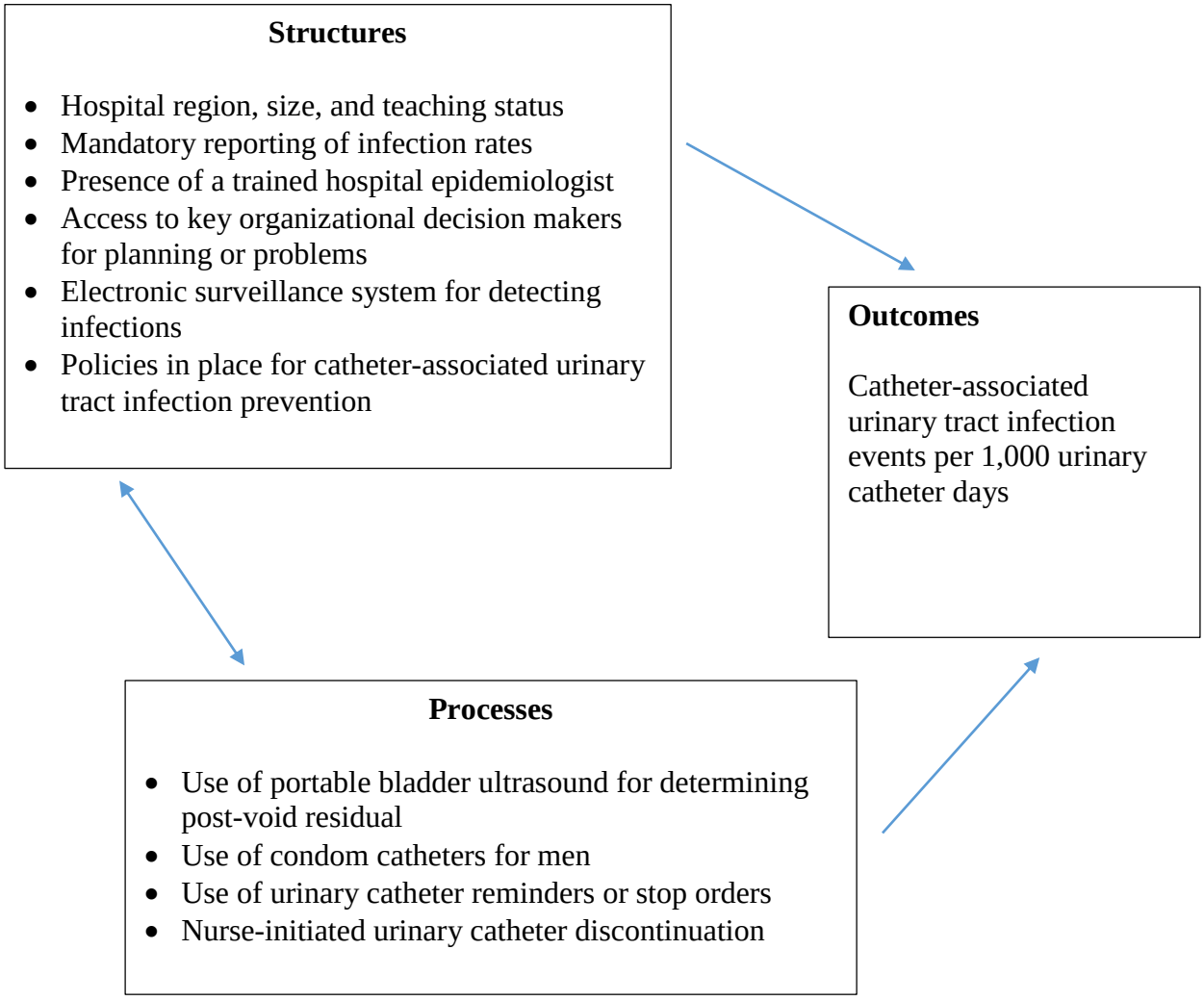
Using these frameworks, this dissertation examines risk factors for bacteremia secondary to CAB and identifies prevalence and predictors of catheter reduction policies at US hospitals. This research is important to nursing, and results may be used by providers and researchers to improve care delivery and advance the science of health care.

Figure 1.1 Adaptation of the Epidemiologic Triad Conceptual Framework* to Study Risks for Bacteremia Secondary to Nosocomial Catheter-Associated Bacteriuria



*Adapted from Clark EG. Natural history of syphilis and levels of prevention. *The British journal of venereal diseases.* Dec 1954;30(4):191-197.

Figure 1.2 Adaptation of Donabedian's Framework for Assessing the Quality of Health Care* to Study the Presence of and Adherence to Catheter Reduction Policies in US Hospitals



*Adapted from Donabedian A. Evaluating the quality of medical care. *The Milbank Memorial Fund quarterly*. Jul 1966;44(3):Suppl:166-206.

Chapter Two: Systematic Review

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

This manuscript is accepted for publication in the journal *Urologic Nursing*.

Abstract

Background: Catheter-associated bacteriuria (CAB) is complicated by bacteremia in 3.6% of patients; attributable mortality is 12.7%. **Purpose:** We conducted a systematic review to identify risk factors for bacteremia secondary to CAB among adults in acute care settings. **Data Sources:** Searches of Medline and 4 other electronic databases were conducted to find original, peer-reviewed research published in English between 1983 and 2014. **Study Selection:** Two researchers screened 5231 titles and abstracts, and 79 full texts, excluding studies that lacked an outcome measure for risk of urinary tract-related bacteremia, studies conducted in long-term care or outpatient settings, studies of renal transplant or urological patients, and studies where less than half the sample had a urinary catheter. **Data Extraction:** Seven studies: 3 observational cohort, 2 case-control, and 2 randomized controlled trials were included. Information on study design, setting, sample, variable definitions, analytics, and findings were systematically collected. The Newcastle-Ottawa Scale and the Cochrane Collaboration tool for assessing risk of bias were used to appraise the quality of evidence. **Data Synthesis:** Weak evidence suggests that male patients who have received immunosuppressant medications or red blood cell transfusion, those not receiving antimicrobials, and those with neutropenia, malignancy, or liver disease may be at increased risk for bacteremia due to CAB. The role of diabetes and underlying urinary tract disease in the causal pathway from CAB to bacteremia is unclear. Findings were heterogeneous due to inconsistent definitions of bacteremia and examination of a wide variety of risk factors. All studies were at high risk of at least one type of bias; however, the case-control studies were more aptly designed and conducted to answer the review question. **Conclusions:** Risks for bacteremia secondary to CAB have been identified but the evidence base is weak.

Background

Each year, more than 13,000 deaths are attributed to healthcare-associated urinary tract infections.[13] The vast majority of infections are associated with urinary catheters.[18] Adult patients with urinary catheters develop bacteriuria at a rate of 8% per day during the first week.[57] One in 27 patients with CAB goes on to develop secondary bacteremia[10] with a seven-day mortality of more than 30%[58] and an attributable mortality rate of 12.7%.[12] The cost of bacteremia due to CAB was conservatively estimated at $2836 per episode in 2000;[10] or approximately $3790 today.[59] The precise link between CAB and bacteremia remains unknown.

Identifying those patients with bacteriuria 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 those patients at highest risk for the most serious sequelae of CAB.[18] 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.[60]

Search Strategy

Electronic searches of Medline, Scopus, the Cochrane Library, the Cumulative Index to Nursing and Allied Health, 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 **Table 2.1**. 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 the 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,[16] and recommendations in subsequent guidelines have changed little over the intervening years.[15] Therefore, clinical research into CAB from 1983 forward is likely applicable to current catheterized patient populations and settings.

Study Selection

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 2.1**. 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.[61] 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 indwelling catheters such as biofilm formation and constant but incomplete evacuation of urine from the bladder may impact the risk for subsequent bacteremia.

Data Extraction

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

Quality Assessment

The quality of included observational studies was appraised using the Newcastle-Ottawa Scale (NOS).[62] The NOS examines threats to validity common to observational studies, namely sampling bias, information bias, and confounding. It is comprised 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.[63] 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.[64] 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 2.1**. Screening of 5231 titles and abstracts and 79 full texts yielded 7 eligible studies.[42,44,46,65-69] Two articles which used the same sample and similar methodology to examine different risk factors are treated as one study for the purposes of this review.[46,67] Although both articles examined risk factors for bacteremia after CAB, one of the articles specifically investigated blood transfusions, and the other explored multiple risk factors but not blood transfusions.

Sample

Characteristics of the three observational cohort,[42,65,66] two case-control,[44,46,67] and two randomized controlled trials (RCTs)[68,69] are outlined in **Table 2.2**. For studies that conducted a subgroup analysis for bacteremia, only the 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,[42,44,46,67-69] one specifically included fungal pathogens,[44] and two studies examined one genus (enterococci)[66] or species (*Staphylococcus aureus*).[65] One study sampled patients with asymptomatic bacteriuria,[69] and the remainder sampled bacteriuric patients with and without urinary tract symptoms. In two studies, 100% of patients had indwelling urinary catheters,[68,69] and in three studies the proportion of patients with catheters was between 57% and 86%.[44,65,66] In the two studies which were missing catheter data all bacteriurias were nosocomial,[42,46,67] so it

was assumed that more than half of the patients had urinary catheters.[18] Five of the seven studies examined only nosocomial infections.[42,44,46,67-69]

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;[69] 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 – 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 2.3, 2.4 and 2.5** 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,[42,65,66] 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 since bacteremia was demonstrated to be present but not absent, and detection bias (e.g., 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.[44] 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 sub-clinical symptoms) would have been misclassified as control patients.[46,67] 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.[68] In the other RCT, patients with recurrent positive urine cultures, who may have been more likely to develop subsequent sepsis were excluded.[69] 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.[44,46,67] 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, and assessment of potential interactions and control for confounding by logistic regression.

Findings

Risks factors for bacteremia identified by the studies are summarized in **Table 2.6**. Male sex was identified as a risk factor in three of four studies.[42,44,46,67] 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;[44,46,67] 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,[44,46,65,67] and the fourth study was likely underpowered to find a difference.[69] 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.[46] Neutropenia from any cause,[67] liver disease,[67] and malignancy[44] each independently increased the risk of developing bacteremia. Risk for bacteremia increased 3% per day of stay prior to CAB.[44] 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,[67] but was non-significant in three others.[42,44,65] 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,[42,68] urological procedure,[67] or surgery.[65] The urinary pathogen *Serratia marcescens* was more prevalent among patients who developed bacteremia compared to those who did not in an uncontrolled study,[42] but pathogen species was not a risk factor in a subsequent study using multivariable analysis,[44] and vancomycin-resistance was not a significant risk factor for bacteremia in a study of enterococcal bacteriuria.[66] Smoking was not associated

with bacteremia in one case-control study,[67] putting into question the weak association identified in an earlier case-control study.[44] Finally, one study identified diabetes mellitus as a risk factor in patients less than 70 years old;[44] whereas, a subsequent study found that receipt of insulin was a risk factor independent of history of diabetes.[67]

Discussion

Results of these studies suggest that males, patients who have received immunosuppressant medications or red blood cell transfusion, those not exposed to antimicrobials, those with neutropenia, malignancy, or liver disease, and those whose stay in hospital prior to CAB was prolonged may be at increased risk for bacteremia secondary to CAB. The potential risks posed by underlying urinary tract disease, urinary tract manipulation, the CAB pathogen, smoking, and diabetes require further study.

The weight and quality of evidence supporting the identified risk factors is 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 >2 or <0.5. It has been suggested that associations identified in observational studies should be considered weak unless the relative risk is >2 or the odds ratio is >3.[70] 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 the 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 asymptomatic 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.[19,20] Since 2009, the Centers for Disease Control and Prevention has included criteria for asymptomatic bacteremic CAB in its surveillance definitions for the National Healthcare Safety Network (NHSN).[71] Hospitals must report these rates for adult and pediatric ICUs through NHSN, in order to fulfill the Centers for Medicare & Medicaid's Hospital Inpatient 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.

Limitations

The 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.[72] Second, our inclusion of only English language studies also may 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.[73] 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.

Conclusions

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.

Table 2.1 Medline Search Strategy Code

Database(s): Ovid MEDLINE(R) 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 "yr =1983 – Current" and "all adult (19 plus years)")

Table 2.2 Characteristics of Included Studies

First Author and Year Published	Design	Aim	Setting	Sample	Age Mean or Median (Range)	Male	Indwelling Urinary Catheter	Definition of Secondary Bacteremia or Sepsis
Krieger[1] 1983	prospective observational cohort	"to identify... particular organisms and patient characteristics which influence the probability of development of secondary bacteremias"	730 bed primary and tertiary care hospital in United States	Patients with nosocomial bacteriuria (>=10^5 cfu/mL or >=10^6 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[2] 1984	retrospective observational cohort	"to describe the role of the urinary tract as the portal of entry for Staph. aureus bacteremia and to define some useful risk factors"	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 - 99)	81%	63%	Signs of generalized infection in combination with positive *S.aureus* blood culture with identical antibiograms and phage type to urine culture, >48 hours after bacteriuria or UTI symptoms preceded simultaneous positive cultures by >48 hrs. N=11
Khair[3] 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"	1250 bed tertiary care hospital in United States	Adult patients with enterococcal bacteriuria, including polymicrobial bacteriuria (>=$5x10^4$ cfu/mL, or >10^5 cfu/mL in patients with a catheter) with or without symptoms of UTI. N=454	65 (17 - 96)	37%	51%	Definition missing. N=8
Saint[4] 2006	matched case control	"investigated the risk factors for developing bacteremia in patients with hospital-acquired bacteriuria"	primary care and referral Veterans Affairs hospital in United States	Adult patients with nosocomial bacteriuria (>=10^5 cfu/mL of a single predominant bacterial or fungal species) with or without symptoms. N=237	66 (26-98)	95%	86%	Blood culture obtained within 30 days of a urine culture that grew the same organism species. N=95
Rogers[5] 2011 and Greene[6] 2012	matched case control	"to examine both previously identified and novel risk factors that may alter the risk of urinary tract related BSI"	800 bed tertiary care referral hospital in United States	Adult patients with nosocomial bacteriuria (>10^5 cfu/mL of a single organism) with or without symptoms of UTI. N=665	60 (21 - 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=198

First Author and Year Published	Design	Aim	Setting	Sample	Age Mean or Median (Range)	Male	Indwelling Urinary Catheter	Definition of Secondary Bacteremia or Sepsis
Karchmer[7] 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 UTIs" vs. a silicone-coated latex catheter	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[8] 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"	tertiary care hospital in France	Adult ICU 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: temp >38C or <36C; HR>90 beats/min; breathing rate >20 cycles/min or PaCO2 <32mmHg or mechanical ventilation; WBC count >12g/L or <4g/L. N=6

1. Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. *J. Infect. Dis.* Jul 1983;148(1):57-62.
2. Arpi M, Renneberg J. The clinical significance of Staphylococcus aureus bacteriuria. *J Urol.* Oct 1984;132(4):697-700.
3. Khair HN, VanTassell P, Henderson JP, Warren DK, Marschall J, Vancomycin resistance has no influence on outcomes of enterococcal bacteriuria. *J Hosp Infect.* Nov 2013;85(3):183-188.
4. 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.* Sep 2006;34(7):401-407.
5. Rogers MA, Blumberg N, Heal JM, et al. Role of transfusion in the development of urinary tract-related bloodstream infection. *Arch Intern Med.* Sep 26 2011;171(17):1587-1589.
6. Greene MT, Chang R, Kuhn L, et al. Predictors of hospital-acquired urinary tract-related bloodstream infection. *Infect Control Hosp Epidemiol.* Oct 2012;33(10):1001-1007.
7. Karchmer TB, Giannetta ET, Muto CA, Strain BA, Farr BM. A randomized crossover study of silver-coated urinary catheters in hospitalized patients. *Arch Intern Med.* Nov 27 2000;160(21):3294-3298.
8. Leone M, Perrin AS, Granier I, et al. A randomized trial of catheter change and short course of antibiotics for asymptomatic bacteriuria in catheterized ICU patients. *Intensive Care Med.* Apr 2007;33(4):726.

UTI, urinary tract infection; cfu/mL, colony forming units per milliliter

Table 2.3 Risks of Bias in Included Observational Cohort Studies*

	Krieger 1983[1]	Arpi 1984[2]	Khair 2013[3]
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., >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

1. Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. *J. Infect. Dis.* Jul 1983;148(1):57-62.
2. Arpi M, Renneberg J. The clinical significance of Staphylococcus aureus bacteriuria. *J Urol.* Oct 1984;132(4):697-700.
3. Khair HN, VanTassell P, Henderson JP, Warren DK, Marschall J, Vancomycin resistance has no influence on outcomes of enterococcal bacteriuria. *J Hosp Infect.* Nov 2013;85(3):183-188.

*Bias assessed using the Newcastle-Ottawa Scale; Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed November 4, 2014.

Table 2.4 Risks of Bias in Included Case-Control Studies*

	Saint 2006[1]	Rogers 2011[2] Greene 2012[3]
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

1. 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.* Sep 2006;34(7):401-407.
2. Rogers MA, Blumberg N, Heal JM, et al. Role of transfusion in the development of urinary tract-related bloodstream infection. *Arch Intern Med.* Sep 26 2011;171(17):1587-1589.
3. Greene MT, Chang R, Kuhn L, et al. Predictors of hospital-acquired urinary tract-related bloodstream infection. *Infect Control Hosp Epidemiol.* Oct 2012;33(10):1001-1007.

*Bias assessed using the Newcastle-Ottawa Scale; Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed November 4, 2014.

Table 2.5 Risks of Bias in Included Randomized Controlled Trials*

	Karchmer 2000[1]	Leone 2007[2]
Random sequence generation	Low risk of bias. Sequence generation was not described, but the cross-over design minimizes risk.	Low risk of bias.
Allocation concealment	Low risk of bias. Allocation concealment is not described, but the cross-over 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 who were 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". 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.

1. Karchmer TB, Giannetta ET, Muto CA, Strain BA, Farr BM. A randomized crossover study of silver-coated urinary catheters in hospitalized patients. *Arch Intern Med.* Nov 27 2000;160(21):3294-3298.
2. Leone M, Perrin AS, Granier I, et al. A randomized trial of catheter change and short course of antibiotics for asymptomatic bacteriuria in catheterized ICU patients. *Intensive Care Med.* Apr 2007;33(4):726.

*Bias assessed using the Cochrane Collaboration Tool for Assessing Risk of Bias; Higgins J, Altman D, Sterne J. Assessing Risk of Bias in Included Studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*: The Cochrane Collaboration; 2011.

Table 2.6 Risk Factors for Bacteremia Secondary to Urinary Catheter-Associated Bacteriuria

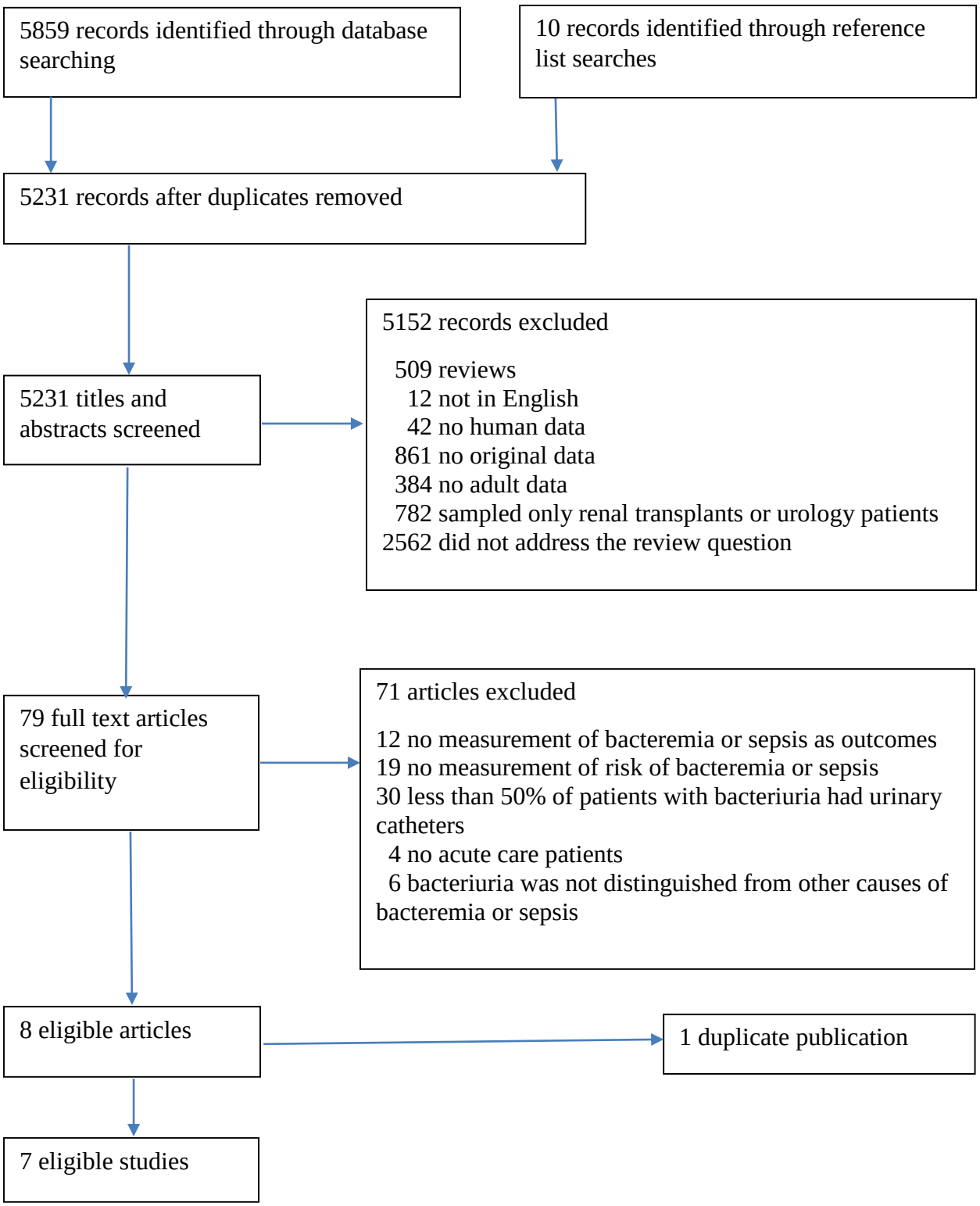
	Unadjusted Analyses			Multivariable Analyses		Randomized Controlled Trials	
	Krieger 1983[1]	Arpi 1984[2]	Khair 2013[3]	Saint 2006[4]	Rogers 2011[5] Greene 2012[6]	Karchmer 2000[7]	Leone 2007[8]
Male sex	Males (3.7%) vs. females (1.6%) p<0.05	NS		OR=1.88 CI 1.62-2.18	OR=2.18 CI 1.52-3.12		
Age	NS	NS		NS	NS		
Race	NS			NS			
Smoking				OR=1.26 CI 1.01-1.57	NS		
Comorbidities	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 <70 years OR=6.19 CI 1.30-29.40 Diabetes is protective if age >=70 years OR=0.11 CI 0.02-0.83 HIV infection NS	Neutropenia OR=10.99 CI 5.78-20.88 Liver disease OR=2.34 CI 1.35-4.06 Diabetes mellitus NS Hypertension NS		
Urinary tract disease	Genitourinary tract disease NS	Obstruction NS		Renal insufficiency NS	Renal disease OR=2.96 CI 1.98-4.41		
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 1.31-4.73	Silver-coated catheter vs. uncoated NS RR=0.56 CI 0.19-1.66	
Antimicrobial		Appropriate (0%) protective vs. inappropriate or none (15.9%) p<0.001		Protective OR=0.76 CI 0.68-0.85	Protective OR=0.66 CI 0.44-0.97		3-day course antibiotic with catheter change vs. standard of care NS p=1.0

	Krieger 1983[1]	Arpi 1984[2]	Khair 2013[3]	Saint 2006[4]	Rogers 2011[5] Greene 2012[6]	Karchmer 2000[7]	Leone 2007[8]
Urinary pathogen	*S.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 2.90-8.06 Platelets, plasma NS		
Immuno-modulating drugs				Immunosuppressants OR=8.13 CI 1.02-64.83 Corticosteroids age <70 years OR=14.24 CI 4.76-42.63 corticosteroids are protective if age >=70 years OR=0.08 CI 0.02-0.34	Immunosuppressants OR=1.53 CI 1.04-2.25 Insulin OR=4.82 CI 2.52-9.21 Statins NS		
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				Per day OR=1.03 CI 1.01-1.04			
Quality score*	4/8	4/8	3/8	7/9	7/9	4/7	5/7

1. Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. *J. Infect. Dis.* Jul 1983;148(1):57-62.
2. Arpi M, Renneberg J. The clinical significance of Staphylococcus aureus bacteriuria. *J Urol.* Oct 1984;132(4):697-700.
3. Khair HN, VanTassell P, Henderson JP, Warren DK, Marschall J, Vancomycin resistance has no influence on outcomes of enterococcal bacteriuria. *J Hosp Infect.* Nov 2013;85(3):183-188.
4. 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.* Sep 2006;34(7):401-407.
5. Rogers MA, Blumberg N, Heal JM, et al. Role of transfusion in the development of urinary tract-related bloodstream infection. *Arch Intern Med.* Sep 26 2011;171(17):1587-1589.
6. Greene MT, Chang R, Kuhn L, et al. Predictors of hospital-acquired urinary tract-related bloodstream infection. *Infect Control Hosp Epidemiol.* Oct 2012;33(10):1001-1007.
7. Karchmer TB, Giannetta ET, Muto CA, Strain BA, Farr BM. A randomized crossover study of silver-coated urinary catheters in hospitalized patients. *Arch Intern Med.* Nov 27 2000;160(21):3294-3298.
8. Leone M, Perrin AS, Granier I, et al. A randomized trial of catheter change and short course of antibiotics for asymptomatic bacteriuria in catheterized ICU patients. *Intensive Care Med.* Apr 2007;33(4):726.

*Higher score = lower risk of bias; bias assessed using the Newcastle-Ottawa Scale or the Cochrane Collaboration Tool for Assessing Risk of Bias for experimental studies; BSI, bacteremia; NS, no significant difference found; OR, odds ratio; CI, 95% confidence interval; ICU intensive care unit

Figure 2.1 Summary of Search and Screening Process



Chapter Three: Case-Control Study

Risk Factors for Secondary Bacteremia in Patients with Catheter-Associated Bacteriuria

This manuscript is planned for submission to the *American Journal of Critical Care* after comment by dissertation committee members.

Abstract

Background: Catheter-associated bacteriuria (CAB) is complicated by secondary bacteremia in 3.6% of cases. The directly attributable mortality rate is 12.7% and the cost per episode is more than $2800. Our aim was to identify risk factors for bacteremia secondary to CAB. **Methods:** We compared case patients with CAB and secondary bacteremia to control patients with CAB and no bacteremia, matched on admission date +/- 30 days. Clinical urine cultures and blood cultures positive for the same pathogen within +7 days were used to define CAB and bacteremia. We queried a large electronic clinical and administrative database of consecutive adult inpatient admissions to 2 acute care hospitals in the Northeast United States between the years 2006 and 2012. Potential risk factors included age, sex, Charlson comorbidity index, diabetes, malignancy, urinary tract disease, urinary tract procedures, facility, length of stay before CAB; receipt of antimicrobials, immunosuppressants or statins before CAB; urinary pathogen and resistance; and presence of a urinary catheter after CAB but before bacteremia in cases or an equivalent time period in matched controls. Multivariable conditional logistic regression was used to determine independent risk factors for bacteremia. **Results:** The sample consisted of 158 cases and 474 controls. Independent predictors of bacteremia were male sex (odds ratio [OR] =2.76; 95% CI, 1.80 – 4.21), receipt of immunosuppressants (OR=1.68; 95% CI, 1.06 – 2.66), urinary tract procedure (OR=2.70; 95% CI, 1.09 – 6.74), and catheter which remained in place after CAB (OR=2.75; 95% CI, 1.65 – 4.56). Patients with enterococcal CAB were half as likely to develop bacteremia as those with other urinary pathogens (OR=0.46; 95% CI, 0.25 – 0.83). The odds of secondary bacteremia increased 2% per additional day of hospital stay (95% CI, 1.01 – 1.04), and decreased 1% with each additional year of age (95% CI, 0.97 – 0.99). **Conclusions:** This research adds new information about the increased risk for bacteremia among patients with

catheters remaining in place after CAB, and adds important confirmatory evidence for previously identified risk factors. Research is needed to clarify the independent effects of age on risk for bacteremia after CAB.

Key Words: urinary catheter, bacteriuria, healthcare-associated infection, urosepsis

Background

Urinary catheters are common in the intensive care unit (ICU); in fact, a majority of adult ICU patients has a urinary catheter in place (50-78%).[3] During the first week of catheterization, 8% of patients per day develop catheter-associated bacteriuria (CAB).[57] The incidence of symptomatic infection ranges from 1.2 – 5.0 per 1,000 catheter days in ICUs in the United States, and as high as 16 per 1,000 internationally.[3,4]

CAB can result in significant morbidity, mortality and cost, particularly if complicated by bacteremia. Prospective studies have found that 0.4% to 4% of patients with CAB progress to bacteremia.[9,10,74] The mortality rate directly attributable to hospital-acquired bacteremic CAB is 12.7%.[12] In the most recent estimate published in 2000, the cost of bacteremic CAB was $2836 per episode.[10]

There is a paucity of evidence concerning risk factors for bacteremia secondary to CAB. A few studies suggest that male patients, patients who have received immunosuppressant medications or red blood cell transfusion, smokers, and patients with neutropenia, malignancy, liver disease, diabetes, or underlying renal disease may be at increased risk for bacteremia.[44,46,67] However, there is conflicting evidence for some risk factors, and others have only been examined in single studies. To our knowledge, the influence of continued catheter presence on the risk for bacteremia has not been studied.

Identifying risk factors for bacteremia would enable clinicians to target interventions such as early catheter removal, or use of alternatives such as intermittent catheterization to patients at highest risk.[75] Distinguishing patients at low risk of bacteremia could reduce inappropriate use of

antimicrobials for asymptomatic bacteriuria.[28] Our aim therefore was to describe risk factors for secondary bacteremia among adult patients with nosocomial CAB.

Methods

We employed a matched case-control design, comparing case-patients with nosocomial CAB and concurrent bacteremia, to control-patients with nosocomial CAB without bacteremia. Three controls were randomly selected from among all patients with CAB who were admitted within 30 days before or after the case patient. Cases and controls were matched on admission date to account for any unmeasured changes in clinical care that occurred over time, such as culturing practices or catheter materials used. Cases and controls were not matched on any other characteristic such as age or length of stay because we wanted to examine the impact of these variables on the risk for bacteremia.

Setting and Sample

Data were obtained from a large database that merged electronic clinical and administrative data for the years 2006 – 2012 from all inpatient admissions to an academic medical system in the Northeast United States.[76] All consecutive admissions of patients $\geq$18 years of age to two hospitals were included. Facility A is a 300-bed community hospital and Facility M is a 745-bed tertiary care hospital. Institutional review board approval was obtained with a waiver of individual consent.

Measures

Results of clinical cultures were used for the study. Nosocomial CAB was defined as a positive urine culture occurring on or after hospital day three in a patient with no previous positive urine culture during the admission, and an indwelling urethral catheter in place on the

date of the culture or within 72 hours before the culture. A positive urine culture was defined as either of the following: $\geq 10^5$ colony forming units per milliliter (cfu/mL) of urine with no more than two species of microorganisms; or $<10^5$ cfu/mL of urine with no more than two species of microorganisms, and pyuria (>3 pus cells per high-powered field) within +/- 48 hours of the positive culture. Our definitions were designed to be as similar as possible to definitions of catheter-associated urinary tract infection in use at the time by the National Healthcare Safety Network (NHSN).[77] The number of cfu/mL is of minor consequence, since the quantity of microorganisms in a catheter specimen of urine is known to increase from as low as 1 cfu/mL to $>10^5$ cfu/mL within 24-48 hours if the patient is not receiving antimicrobials to which the organism is susceptible.[78] Only the first CAB event was included for each patient. Concurrent bacteremia was defined as growth of the same species from a blood culture taken within 7 days after the urine culture, in a patient who had had no previous blood cultures positive for the same organism during the same admission. Pathogens were identified and sensitivity to antimicrobials was determined using conventional microbiological methods.

The Charlson Comorbidity Index was used to measure comorbidities in the aggregate on admission.[47] The presence or absence of diabetes mellitus, malignancy, or urinary tract disease was identified using primary or secondary International Classification of Diseases, 9th revision, Clinical Modification (ICD-9) codes with present on admission indicators. Electronic medication administration records were used to ascertain whether or not a patient received antimicrobials within three days before CAB, immunosuppressants including steroids up to 14 days before CAB, or hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins) within six weeks before CAB during the current admission. ICD-9 procedural codes were used to identify whether

or not a patient had undergone a urinary tract procedure or surgery at any time during their admission.

Age, sex, facility, and length of stay were determined using electronic administrative data. Number of days of catheterization before CAB was calculated using the electronic clinical record for cases and controls. To assess the effect of leaving a catheter in place after CAB onset on the risk of developing bacteremia, we identified whether a catheter was present or absent on the day of bacteremia in the cases, and after an equivalent period of time in the matched controls. Thus, if a case developed bacteremia two days after CAB, we looked for the presence or absence of a catheter in the matched controls two days after their CAB dates.

Analysis

Descriptive statistics were computed for cases and controls separately, including means and standard deviations or medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. Simple and multivariable conditional logistic regression models were constructed. The outcome bacteremia was regressed on each of the risk variables in simple logistic models. Any variable with $p \leq 0.25$,[79] or that was clinically relevant was entered into a preliminary multivariable model, and any variable with $p > 0.05$ that was not a confounder in the preliminary model was removed. To examine whether the effects of the continuous variables on the outcome bacteremia were linear on the logit scale, each was transformed into a categorical variable based on quartiles, and a plot was visually inspected. Unless the transformed term had a more significant relationship with bacteremia than the continuous term in a regression model, the continuous term was retained. Potential interactions were tested using the Wald Chi-square test, including malignancy with immunosuppression, and age with each of the following: Charlson index, diabetes, malignancy, urinary tract disease,

immunosuppressant, or urinary tract procedure. Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

During the study period, there were 158 cases of CAB with secondary bacteremia. Approximately half (53%) of the cases had urine and blood cultures positive on the same day. Three controls were identified for each case, bringing the total sample to 632 patients. The distributions of risk factors among cases and controls are listed in **Table 3.1**. Cases were significantly younger than controls (median age 66 vs. 70 years, $p=0.03$), but had a higher comorbidity index (3 vs. 2, $p=0.02$). Among cases, there was a higher proportion of males (59% vs. 35%, $p<0.0001$), and patients with malignancy (28% vs. 18%, $p=0.005$). More cases received antimicrobials (49% vs. 35%, $p=0.002$) and immunosuppressants (42% vs. 27%, $p=0.0005$) than controls. Urinary tract procedures were more common among cases than controls (11% vs. 4%, $p=0.001$). Cases had a longer hospital stay (10 days vs. 7 days, $p<0.0001$) and had catheters in place for longer periods before CAB than controls (8 vs. 4 days, $p<0.0001$).

More cases had catheters in place at the time of bacteremia than did controls at an equivalent time period (79% vs. 56%, $p<0.0001$). To illustrate this point further, **Figure 3.1** shows the percent of cases and controls with a catheter left in place after developing CAB. Cases who developed bacteremia and their matched controls were removed from the denominator for subsequent days. On the day of positive urine culture (day 0), 84% of cases and 68% of controls had a catheter in place. On subsequent days, more than 70% of cases who had not yet developed bacteremia still had a catheter in place, while a steadily declining proportion of their matched controls had a catheter in place.

A single organism was responsible for CAB in most patients (96%). **Table 3.2** lists causative organisms for CAB and bacteremia. The most common urinary pathogens were Enterobacteriaceae (*E.coli* 34%; *K.pneumoniae* 17%); and *Enterococcus* spp. (*E.faecalis* 14%; *E.faecium* 5%). CAB caused by *Klebsiella* was more common among cases than controls (27% vs. 16%, p=0.005), and enterococcal CAB was less common among cases (14% vs. 23%, p=0.02). There was no significant difference in the proportion of resistant urinary pathogens between cases and controls (10% vs. 9%).

Results of a conditional logistic regression model are displayed in **Table 3.3**. Catheter days and length of stay were found to be collinear; therefore, only length of stay was included in the model. The final model included age, sex, Charlson index, diabetes, malignancy, urinary tract disease, immunosuppressant medication, urinary tract procedure, *Enterococcus* in urine, *Klebsiella* in urine, length of stay before CAB, and catheter in place after CAB. No significant interactions were found. Controlling for other factors in the model, the odds of bacteremia were more than two and a half times higher for males than females (odds ratio [OR] =2.76, 95% CI 1.80 – 4.21), for patients who underwent a urinary tract procedure (OR=2.70, 95% CI 1.09 – 6.74), and for those with a catheter left in place (OR=2.75, 95% CI 1.65 – 4.56). Patients on immunosuppressants had 1.7 times the odds of developing bacteremia (95% CI 1.06 – 2.66). Patients with enterococcal CAB were half as likely to develop bacteremia as patients with CAB caused by other genera (OR=0.46, 95% CI 0.25 – 0.83). The odds of developing secondary bacteremia increased 2% per additional day of stay in hospital before CAB onset (95% CI 1.01 – 1.04), and decreased 1% with each addition year of age (95% CI 0.97 – 0.99).

Discussion

Our study identified several independent predictors of bacteremia in patients with CAB; younger age, male sex, immunosuppressant medication, urinary tract procedure, non-enterococcal CAB, longer hospital stay before CAB, and catheter in place after CAB. These findings reinforce previous research and also identify catheter presence as a risk factor not previously reported.

We found a 1% decline in risk of bacteremia with each additional year of age. This is puzzling because it contradicts theories of immunosenescence.[80] However, it is consistent with findings from two previous case-control studies that examined risks for nosocomial urinary tract-related bacteremia. In one, cases were significantly younger than controls in unadjusted analysis.[67] In the other, diabetes and steroid use were predictors of bacteremia only in patients younger than 70 years.[44] It is generally thought that older people are more vulnerable to infection, but in a recent study using a national random sample of hospitalized adults, age was not associated with overall rates of healthcare-associated infections (HAI) after controlling for other demographic characteristics, device use, and common comorbidities.[81] Further, two recent hospital studies that found higher HAI rates among patients over 65 years of age, also found significantly higher urinary catheter utilization among the elderly.[82,83] It is possible that by sampling only catheterized patients we eliminated a confounding influence not controlled for in earlier work. The relationship between age and risk of infection warrants more research.

Although women are known to be at increased risk for CAB,[81] men have been shown to be at increased risk for bacteremia secondary to CAB.[42,44,67] In our study, the odds of bacteremia were 2.8 times higher for men, supporting the earlier results. In a related study, we found men were also at increased risk for surgical site infection and primary bloodstream infection (i.e.,

bacteremia without cultures positive for the same organism from another body site).[84] The increased risk for bacteremia secondary to CAB in men compared to women may be due to hormonal differences, differences in genitourinary anatomy or the indication for catheterization (e.g., obstruction), or differences in the urinary microbiota between the sexes.[85] These potential underlying mechanisms deserve further investigation.

Not surprisingly, we found that patients who received immunosuppressant medication were at increased risk for bacteremia, confirming earlier evidence.[44,67] Also as expected, we found patients with CAB who underwent urological procedures were at risk for bacteremia. Previous studies have demonstrated that procedures that injure the mucosal barrier, such as transurethral prostate resection promote translocation of pathogens to the bloodstream increasing the chance of bacteremia and sepsis.[67,86,87]

The prevalence of urinary pathogens and proportion of resistant organisms in our study was similar to that reported in 2009-2010 to NHSN for symptomatic and bacteremic urinary tract infection.[88] The four most common pathogens identified in our study were among the top five most common urinary pathogens reported to NHSN. Candida species was the exception, comprising about 13% of causative organisms in the national sample, but only 0.15% (n=1) of our sample. This could be because 65% of HAIs in the NHSN sample occurred in ICUs, where candiduria is more common than in the hospital population overall.[89] In our sample, the proportion of *Staphylococcus aureus* isolates resistant to methicillin (40%) and *Enterococcus* resistant to vancomycin (*E.faecalis* 8%, *E.faecium* 89%) matched NHSN prevalence; however, the proportion of enterobacteriaceae producing extended-spectrum β lactamase (ESBL) was smaller in our sample than in the NHSN report (*Escherichia coli* ESBL 5% vs. 12%; *Klebsiella pneumoniae/oxytoca* ESBL 3% vs. 27%).[88] We did not find resistance to be a predictor of

bacteremia. This confirms a previous prospective study which found no difference in bacteremia outcomes for patients with vancomycin resistant versus sensitive enterococcal bacteriuria.[66]

We did find that the odds of bacteremia were 54% lower in patients with CAB caused by *Enterococcus* compared to other pathogens. This adds a measure of clarity to equivocal results from the two studies referred to earlier. In the first, *Enterococcus* species were significantly less common among case-patients who developed bacteremia than among controls.[44] In contrast, the second study found *Enterococcus* species were significantly more common among cases.[67] However, these differences were not statistically significant in adjusted analysis in either study. Similarly, in a large prevalence study of nosocomial CAB in hospitalized urology patients across Europe and Asia, enterococcal infections were no less likely to present as urosepsis than infections caused by other pathogens.[90] Thus our finding of an independent effect is new, and the reasons why patients with enterococcal CAB might be less likely to develop bacteremia are unclear. It is possible that the odds of enterococcal bacteremia are lower in populations where resistance to vancomycin in enterococcal urinary isolates is low (ours was 30% compared to 57% in the study by Greene et al.),[67,91] yielding more protection from empiric or concurrent antimicrobials. Further evidence is needed from studies that consider the match between the urinary pathogen and the antimicrobial prescribed, rather than receipt of antimicrobials in general.

Our results suggest that longer length of stay before CAB increases risk for bacteremia, reinforcing previous research.[44] Length of stay before CAB may be a proxy for patients' severity of illness; if so, it makes intuitive sense that patients who have been in hospital longer are more likely to develop bacteremia.

To our knowledge, our study is the first to examine the influence of continued catheter presence on the risk for bacteremia in patients with CAB. The odds of bacteremia were higher for patients with a catheter left in place after the onset of CAB, taking into account age, sex, comorbidities, medications, procedures, pathogen, and length of stay. An association is plausible, because urinary catheters develop biofilms that insulate pathogens physically and slow their replication, minimizing the effects of antimicrobials.[92] Also, latex and silicone have been shown to cause inflammation and cell membrane disruption of urothelial cells in the presence or absence of bacteria in vitro.[93,94] This physical and chemical irritation of the bladder epithelium by catheters may promote translocation of pathogens from the urine into the bloodstream. However, it is possible that in our sample patients with catheters remaining in place were more acutely ill than those with catheters removed. Although we controlled for comorbidities using the Charlson index, we were not able to control for severity of illness at the time of CAB, thus catheter presence may be a proxy for patient acuity.

Several comorbidities which were previously identified as risk factors for bacteremia in patients with CAB were not supported by our results. A least one previous study has noted increased odds of bacteremia for patients with malignancy,[44] urinary tract disease,[67] diabetes,[44] or higher Charlson comorbidity score;[95] whereas these differences were not apparent in our results.

Limitations

Our results must be considered in light of several limitations. First, although our case-control design was appropriate for examining risk factors for this rare outcome, we are not able to infer causality. Second, because the data were retrospective, the quality of the measures may be imperfect (e.g., coding of comorbidities may have been incomplete or clinical specimens may

have been collected incorrectly). Third, there is a possibility of misclassification bias. Patients classified as having had a urological procedure may have undergone the procedure after the CAB event and the seven day follow-up period. This misclassification of exposure would have been non-differential, thus biasing results toward the null. Also, we drew our control patients from among all patients without a positive blood culture. By doing so, our pool of controls may have included patients who were clinically septic but did not have blood cultures drawn or had negative blood cultures because of collection or culturing techniques, timing, or receipt of antibiotics. In effect, we may have compared cases of bacteremia to cases of sepsis. To avoid this misclassification, other studies have selected controls from among patients for whom a blood culture was not obtained, indicating the provider does not suspect sepsis.[44] We consider this solution unacceptable because it biases the results toward finding spuriously large differences, since the population from which controls are drawn is less severely ill than the cases. Also, it ignores a key principle of case-control methodology; that is, that cases and controls should arise from the same population.[96] In post-hoc analysis using ICD-9 codes for sepsis, severe sepsis, and septic shock, we found that 41% of cases and only 7% of controls were septic during their hospitalization (data not shown), reassuring us that misclassification was minimal if present. Fourth, unmeasured factors such as smoking, genetic predisposition to infection, or blood transfusion history may have confounded our results. Transfusion of red blood cells has a strong, dose-dependent effect on risk for urinary tract-related bacteremia,[46] and restricting transfusions lowers HAI risk.[97] Finally, the sample is from two hospitals in a metropolitan academic medical system, so results may not be generalizable to patients in small or rural hospitals.

Implications

Despite these limitations, our findings are useful for informing clinical practice. Males with urinary catheters who are receiving immunosuppressant medication, who have had a urinary tract procedure, or who have been in hospital for a prolonged period, and who have non-enterococcal CAB should be considered high risk for bacteremia. These patients should be targeted for early catheter removal or replacement with an alternative such as intermittent catheterization.[75] Suprapubic catheterization could be considered for short-term bladder drainage in adults with multiple risk factors.[75] Condom drainage may be a useful alternative for cooperative patients without outlet obstruction. Although episodes of bacteriuria may not be reduced with the use of a condom device,[98] switching from an indwelling to an external catheter will remove one of the risk factors for associated bacteremia identified in this study.

Our findings also may help reduce inappropriate use of antimicrobials by distinguishing patients with CAB who are at low risk for bacteremia. Urinary tract infection is the second most common indication for antimicrobial use in hospitalized patients.[27] Despite expert recommendations against treatment for most asymptomatic infection, 32% of patients with asymptomatic CAB are inappropriately treated.[28,30] Distinguishing risk factors for bacteremia, as we have done, may encourage clinicians to refrain from treating asymptomatic CAB in patients without risk factors.

Conclusions

This research adds new information about the increased risk for bacteremia among patients with catheters remaining in place after CAB, and adds important confirmatory evidence for previously identified risk factors, including male sex, receipt of immunosuppressants, urinary tract procedure, and prolonged length of stay in hospital. Patients with CAB caused by

enterococcus appear to be at lower risk for bacteremia than those with other urinary pathogens. Research is needed to clarify the independent effects of age on risk for bacteremia after CAB.

Table 3.1 Frequencies of Risk Factors for Bacteremia among Cases and Controls with Catheter-Associated Bacteriuria (CAB)

Variable	Cases n=158	Controls n=474	P-value*
Age (median [IQR])	66 (52-77)	70 (58-80)	**0.03**
Male sex	93 (58.86)	165 (34.81)	**<.0001**
Charlson index (median [IQR])	3 (1-5)	2 (1-4)	**0.02**
Diabetes mellitus	36 (22.78)	139 (29.32)	**0.11**
Malignancy	45 (28.48)	85 (17.93)	**0.005**
Urinary tract disease	92 (58.23)	254 (53.59)	0.31
Antimicrobial within 3 days before CAB	77 (48.73)	165 (34.81)	**0.002**
Immunosuppressant within 14 days before CAB	66 (41.77)	126 (26.58)	**0.0005**
Statin within 6 weeks before CAB	58 (36.71)	194 (40.93)	0.35
Urinary tract procedure	17 (10.76)	18 (3.80)	**0.001**
Resistant organism in urine	16 (10.13)	41 (8.65)	0.57
Two organisms in urine	4 (2.53)	22 (4.64)	**0.25**
Enterococcus in urine	22 (13.92)	107 (22.57)	**0.02**
Escherichia in urine	56 (35.44)	169 (35.65)	0.96
Klebsiella in urine	42 (26.58)	78 (16.46)	**0.005**
Facility A (vs. M)	20 (12.66)	50 (10.55)	0.46
Length of stay before CAB (median [IQR])	10 (5-22)	7 (5-12)	**<.0001**
Catheter days before CAB (median [IQR])	8 (3-20)	4 (2-8)	**<.0001**
Catheter in place after CAB	125 (79.11)	266 (56.12)	**<.0001**

Frequencies are n (%) unless otherwise stated; IQR=interquartile range

*P-values determined by simple logistic regression

Table 3.2 Causative Organisms for Catheter-Associated Bacteriuria and Secondary Bacteremia among 632 Hospitalized Adults

Organism*	Urine n=658[§]			Blood n=158		
	Sensitive	Resistant[£]	Total	Sensitive	Resistant[£]	Total
Escherichia coli	213 (32.37)	12 (1.82)	225 (34.19)	52 (32.91)	3 (1.90)	55 (34.81)
Klebsiella pneumoniae	109 (16.57)	3 (0.46)	112 (17.02)	39 (24.68)	1 (0.63)	40 (25.32)
Enterococcus faecalis	85 (12.92)	7 (1.06)	92 (13.98)	11 (6.96)	2 (1.27)	13 (8.23)
Pseudomonas aeruginosa	43 (6.53)	0	43 (6.53)	9 (5.70)	0	9 (5.70)
Enterococcus faecium	4 (0.61)	32 (4.86)	36 (5.47)	1 (0.63)	8 (5.06)	9 (5.70)
Proteus mirabilis	35 (5.32)	0	35 (5.32)	4 (2.53)	0	4 (2.53)
Enterobacter cloacae	18 (2.74)	0	18 (2.74)	5 (3.16)	0	5 (3.16)
Morganella morganii	12 (1.82)	0	12 (1.82)	1 (0.63)	0	1 (0.63)
Citrobacter koseri	11 (1.67)	0	11 (1.67)			
Staphylococcus aureus	6 (0.91)	4 (0.61)	10 (1.52)	5 (3.16)	2 (1.27)	7 (4.43)
Enterobacter aerogenes	9 (1.37)	0	9 (1.37)			
Serratia marcescens	9 (1.37)	0	9 (1.37)	3 (1.90)	0	3 (1.90)
Citrobacter freundii	8 (1.22)	0	8 (1.22)	1 (0.63)	0	1 (0.63)
Klebsiella oxytoca	8 (1.22)	0	8 (1.22)	1 (0.63)	0	1 (0.63)
Other	30 (4.56)	0	30 (4.56)	10 (6.33)	0	10 (6.33)
Total	600 (91.19)	58 (8.81)	658 (100)	142 (89.87)	16 (10.13)	158 (100)

*Organisms comprising <1% of the sample are listed as other;

[§]26 patients had 2 causative organisms in urine

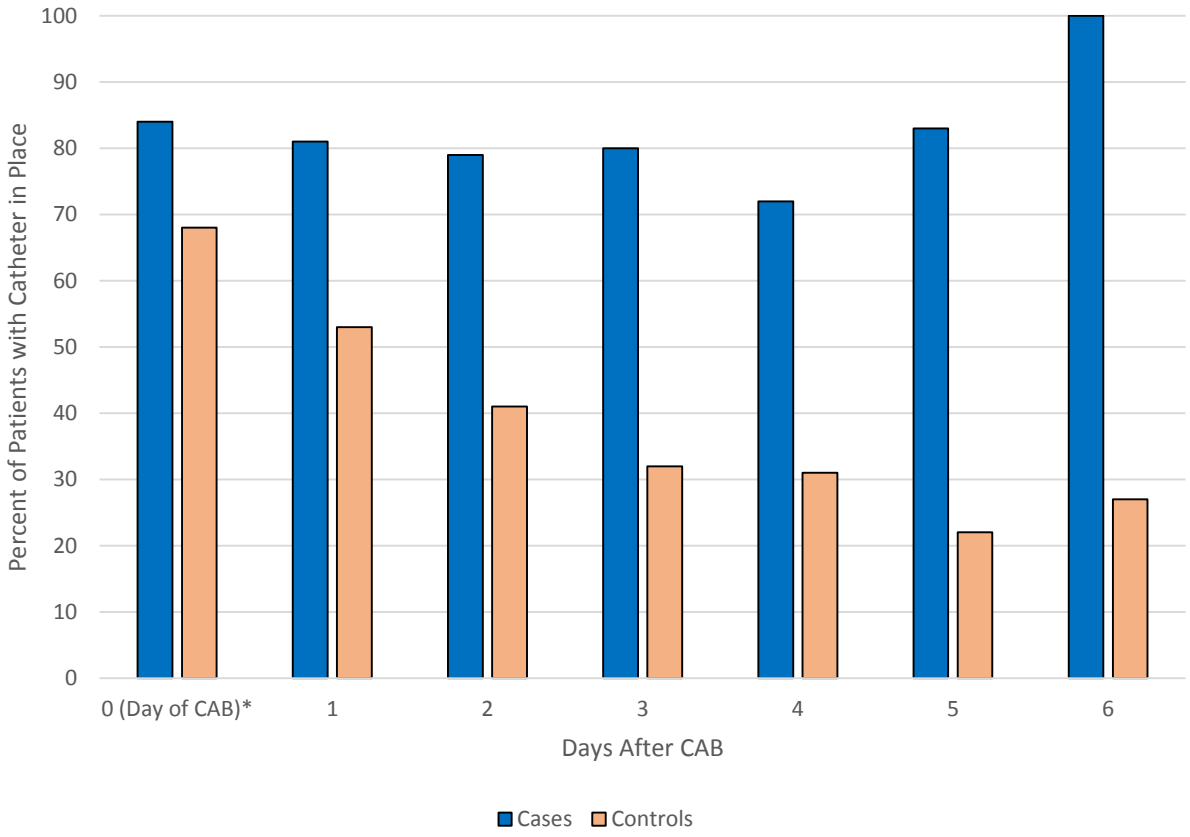
[£]Including extended-spectrum β lactamase Enterobacteriaceae, Methicillin-resistant *Staphylococcus aureus,* and Vancomycin-resistant Enterococcus

Table 3.3 Risk Factors for Bacteremia after Catheter-Associated Bacteriuria (CAB)

Variable	Odds Ratio*	95% CI	p-value
Age	**0.99**	**0.97 – 0.99**	**0.049**
Male sex	**2.76**	**1.80 – 4.21**	**<0.0001**
Charlson index	1.04	0.94 – 1.16	0.42
Diabetes mellitus	0.70	0.42 – 1.18	0.18
Malignancy	1.59	0.88 – 2.88	0.12
Urinary tract disease	0.86	0.54 – 1.35	0.50
Immunosuppressant within 14 days before CAB	**1.68**	**1.06 – 2.66**	**0.03**
Urinary tract procedure	**2.70**	**1.09 – 6.74**	**0.03**
Enterococcus in urine	**0.46**	**0.25 – 0.83**	**0.01**
Klebsiella in urine	1.35	0.78 – 2.35	0.28
Length of stay before CAB	**1.02**	**1.01 – 1.04**	**0.003**
Catheter in place after CAB	**2.75**	**1.65 – 4.56**	**<0.0001**

*A conditional logistic regression model was comprised of the 12 variables listed
CI, confidence interval

Figure 3.1 Percent of Cases and Controls with a Catheter in Place after Catheter-Associated Bacteriuria (CAB) Among Cases Still at Risk for Bacteremia and Their Matched Controls



*16% of cases and 32% of controls developed CAB within 72 hours after catheter removal

Chapter Four: Survey

Adoption of Policies to Prevent Catheter-Associated Urinary Tract Infections in US Intensive Care Units

The contents of this chapter are the peer reviewed version of the following publication:

Conway LJ, Pogorzelska M, Larson EL, Stone PW. (2012). Adoption of policies to prevent catheter-associated urinary tract infections in US intensive care units. Amer Journal Infect Control 2012; 40(8):705-710. PMCID: PMC3644850

The pdf may be accessed at

http://www.sciencedirect.com/science/article/pii/S0196655311012569.

Abstract

Background: Little is known about whether recommended strategies to prevent catheter-associated urinary tract infection (CAUTI) are being implemented in intensive care units (ICU) in the United States (US). **Objectives:** To describe the presence of and adherence to CAUTI prevention policies in ICUs, to identify variations in policies based on organizational characteristics, and to determine if a relationship exists between prevention policies and CAUTI incidence rates. **Methods:** 441 hospitals that participate in the National Healthcare Safety Network were surveyed in spring 2008. **Results:** 250 hospitals provided information for 415 ICUs (response rate 57%). A small proportion of ICUs surveyed had policies supporting bladder ultrasound (26%, n=106), condom catheters (20%, n=82), catheter removal reminders (12%, n=51), or nurse-initiated catheter discontinuation (10%, n=39). ICUs in hospitals with $\geq$500 beds were half as likely as those in smaller hospitals to have adopted at least 1 CAUTI prevention policy (OR=0.52, CI 0.33-0.86), and ICUs in hospitals where the infection control director reported always having access to key decision makers for planning were more than twice as likely as those with less access to have adopted a policy (OR=2.41, CI 1.56-3.72). **Conclusions:** Little attention is currently placed on CAUTI prevention in ICUs in the US. Further research is needed to elucidate relationships between adherence to CAUTI prevention recommendations and CAUTI incidence rates.

Keywords: Catheter-associated urinary tract infection, prevention, infection control, critical care, policy.

Background

Catheter-associated urinary tract infections (CAUTI) are a common and costly occurrence in US hospitals.[13,99] In intensive care units (ICUs) in the US, the incidence rate ranges from 3.1 – 7.4 CAUTI per 1,000 urinary catheter days.[100]

Multiple public policy incentives and private sector quality initiatives are aimed at reducing CAUTI and its resultant morbidity, mortality and cost. Several evidence-based CAUTI prevention guidelines, compiled by panels of experts in infection control and hospital epidemiology have been published over the past 30 years.[16,18,19,101-103] These guidelines all point to one overriding principle – minimize unnecessary urinary catheter use. Many of the strategies advocated in the guidelines support this principle, including substituting condom catheters for indwelling catheters,[16,18,19,103] using bladder ultrasound scanners to identify or rule out urinary retention,[18,19,103] and using automated reminders, stop orders, or nurse-driven protocols to ensure catheters are discontinued as soon as they are no longer needed.[18,19,103] Successive guidelines have become more directive and specific in their call for monitoring adherence to CAUTI prevention practices as well as CAUTI incidence rates.[18,19,101-103] The consistency of these guidelines over time provides a solid basis for CAUTI prevention programs and policies. There is, however, a paucity of research regarding whether or not the practices endorsed in the guidelines are being implemented in ICUs. The aims of this study were 3-fold; (1) to describe the presence of and adherence to CAUTI prevention policies in ICUs in US hospitals, (2) to identify variation in policies based on setting characteristics, infection prevention and control (IPC) department characteristics, and organizational support, and (3) to determine if a relationship exists between prevention policies and CAUTI rates.

Methods

The data were obtained from a large nation-wide, cross-sectional survey of IPC departments designed to examine the cost-effectiveness of infection prevention and control practices (Prevention of Nosocomial Infection and Cost Effectiveness Analysis, National Institutes of Health, R01NR010107). Study procedures were reviewed and approved by institutional review boards at Columbia University, the Centers for Disease Control and Prevention, and RAND Corporation. Sample and recruitment, as well as survey development, content, and pilot testing are described elsewhere[54] and summarized briefly here.

Sample

The National Healthcare Safety Network (NHSN) was used as a sampling frame. NHSN is a network of hospitals that voluntarily or by state mandate confidentially submit data on device-associated healthcare-associated infections (HAI) at their facility for aggregation into a national database for the purposes of trending, benchmarking and in some states public reporting.[104] Hospitals that collect and submit data do so using standardized methods and definitions that include both laboratory and clinical criteria. Hospitals in which NHSN device-associated infection surveillance was conducted according to protocol[105] in an adult medical, surgical, or medical/surgical ICU in 2007 and had at least 500 device-days per year in at least 1 ICU were invited to participate. There were 441 hospitals that met eligibility criteria. IPC department managers or directors of qualifying hospitals were recruited using a modified Dillman technique.[106] The survey was conducted online in spring 2008.

Measures

The survey was developed by adapting a questionnaire used in the Study on the Efficacy of Nosocomial Infection Control.[107] Survey content was validated by a panel of individuals with

expertise in infection control, hospital epidemiology, and psychometrics. A paper version of the survey was pilot tested in 13 different settings and took an average of 27 minutes (SD ±11) to complete. Test-retest reliability showed adequate agreement (mean K=0.88, SD ±0.24). Criterion-referenced validity was assessed by comparing survey responses to institutional policies and data during site visits; no discrepancies were found.

Variables included facility characteristics, IPC department characteristics, organizational support, presence of CAUTI prevention policies, adherence to policies, and CAUTI incidence rates. Facility characteristics included region, number of beds, teaching status, ICU type, and state mandatory reporting of any HAI. IPC department characteristics were assessed with questions about the number and roles of professional staff, board certification in infection prevention and control, and hours dedicated to the IPC department. Organizational support was assessed through questions about access to key decision makers and the use of electronic surveillance systems to track HAIs.

CAUTI prevention policies were assessed with questions about the presence of policies for 4 specific CAUTI prevention strategies: use of condom catheters for men, use of portable bladder ultrasound scanners for determining post-void residual, use of urinary catheter reminders or stop-orders, and nurse-initiated urinary catheter discontinuation. Adherence to policy was assessed by asking respondents what proportion of time each policy was properly implemented: all of the time (95-100%), usually (75-94%), sometimes (25-74%), rarely/never (<25%), or don't know. To assess CAUTI rates respondents were asked to provide incidence data for any medical, surgical, or medical/surgical ICU at their facility. NHSN surveillance definitions in use during the study period are detailed elsewhere.[77] The sensitivity and specificity of urinary tract infection reporting using the NHSN definitions has been reported to be 59% and 98.7% respectively.[108]

Data Analysis

Data analysis was conducted using SPSS Version 19 (SPSS Inc., Chicago IL). Descriptive statistics including frequencies and percentages were used to summarize facility and IPC department characteristics and the adoption of CAUTI prevention policies. Mean and median CAUTI rates were calculated by type of ICU. Staffing ratios were calculated per 100 beds. Bivariate analyses using chi-square tests were conducted to examine associations between facility and IPC department characteristics and the presence or absence of CAUTI policies (i.e., having at least 1 of 4 CAUTI policies in place versus none). Variables that demonstrated significant association with having at least 1 of 4 CAUTI policies in place at the $p<0.10$ level were entered into a multivariable logistic regression model. Odds ratios with 95% confidence intervals were calculated to predict factors associated with adopting CAUTI policies. Lastly, associations between the presence of CAUTI policies, factors predictive of CAUTI policy adoption, and ICU CAUTI rates were examined using Mann-Whitney tests for bivariate analysis and generalized linear regression with log link function for multivariable analysis. Rate ratios with 95% confidence intervals were then calculated to predict factors associated with lower or higher CAUTI rates. All tests were 2-tailed and the significance level was set at $\alpha \leq 0.05$.

Results

There were 250 hospitals that responded to the survey (57%) and provided data on 415 ICUs. The majority of hospitals (56%, n=140) provided data for 1 ICU. **Table 4.1** summarizes sample characteristics. The largest proportion of ICUs was from the Northeast region of the US (41.2%, n=171). More than half of the ICUs were in hospitals with 201-500 beds (54.9%, n=228) and most were in teaching hospitals (71.3%, n=296). Compared to NHSN hospitals[104] and consistent with our eligibility criteria of >500 device days, our sample included a larger

proportion of hospitals with >500 beds (29.7% vs. 15.8% NHSN, $p<0.05$), and teaching hospitals (71.3% vs. 51.7% NHSN, $p<0.05$). There were more medical-surgical ICUs (53.7%, n=223), than either medical (24.9%, n=103) or surgical (21.4%, n=89) units. A majority were in states that required HAI reporting (63.4%, n=251).

Median staffing for IPC departments was 0.61 full-time equivalent infection preventionists (IP) per 100 beds (range 0-4.75). Forty-three percent of ICUs were in hospitals where more than half the IPs were board certified (n=160), while one quarter of the ICUs were in hospitals without a board certified IP (n=95). A large proportion of ICUs were in facilities without a hospital epidemiologist (HE; 42.1%, n=170); of the remainder, only 8.2% (n=33) reported a full-time HE. A majority of respondents described always having access to key organizational decision makers for problems (60.2%, n=250), while a minority described always having access for planning (39.5%, n=163). Less than a third (28.9%, n=118) used an electronic surveillance system to track HAI.

Presence of and Adherence to Policies

CAUTI prevention policies were uncommon in the ICUs surveyed (**Table 4.2**). Policies supporting clinician use of portable ultrasound were in place in 25.9% of ICUs (n=106), while policies promoting the use of condom catheters for men were in place in 20% of ICUs (n=82). Urinary catheter reminders or stop orders, and nurse-initiated urinary catheter discontinuation were infrequently in place (12.4%, n=51; and 9.5%, n=39 respectively). Thirty-one percent of ICUs with urinary catheter reminders or stop orders in place tracked them (n=16), while less than 20% of ICUs tracked any other policy. For any single policy, 5 ICUs or fewer reported $\geq$95% compliance. Less than half the ICUs surveyed reported having at least 1 of the 4 CAUTI policies in place (42.2%, n=174).

Variation in Policies

In bivariate analysis, factors significantly associated with having at least 1 CAUTI prevention policy in place included region, presence of an HE, and access to key decision makers (**Table 4.3**). A larger proportion of ICUs in the West or Midwest had at least 1 CAUTI policy in place than those in the Northeast or South (55.6% and 50% vs. 39.2% and 36.8%, p=0.04). More ICUs supported by a full-time HE had a policy in place than those with a part time HE or no HE (68.8% vs. 36.2% or 44.3%; p=0.002). More ICUs in organizations where the IPC director always had access to key decision makers for planning or problems had a policy in place than those who had access most of the time, sometimes, rarely, or never (55.3% vs. 34.8%, p<0.001 for planning; 47.5% vs. 35.4%, p=0.015 for problems). Small hospital size and use of an electronic surveillance system were associated with having at least 1 CAUTI policy in place, but did not reach statistical significance. No significant differences were found in policy adoption across the following characteristics: teaching status, ICU type, state mandatory reporting, IP staffing levels, or board certification in infection control.

The presence of a full-time HE and hospital region were not significant predictors of policy adoption once adjusted for other factors such as hospital size. In multivariable analysis, only 2 factors predicted policy adoption. ICUs in hospitals where the IPC director always had access to key decision makers for planning were more than twice as likely as those with limited access to have adopted a policy (OR=2.41, CI 1.56-3.72) and ICUs in hospitals with >500 beds were half as likely as those in smaller hospitals to have adopted at least 1 CAUTI prevention policy (OR=0.52, CI 0.33-0.86) after controlling for region, presence of a HE, access to key decision makers for problems, and use of an electronic surveillance system.

CAUTI Rates

Forty-one percent of ICUs (172/415) monitored CAUTI incidence rates; the pooled mean was 3.7 infections per 1000 urinary catheter days (SD 3.39). Median CAUTI incidence rates by ICU type were similar to those reported to NHSN from 2006 through 2008 (**Table 4.4**), falling between the 25th and 75th percentile for each unit type.[100] We found no significant difference in mean CAUTI rates for ICUs with at least 1 policy in place compared to those with no policy (p=0.84). Since hospital size and access to key decision makers for planning were associated with policy adoption, we examined their association with CAUTI rates. In bivariate analysis, hospitals with >500 beds had significantly higher mean (median) CAUTI rates than hospitals with ≤500 beds (4.9 [4.1] vs. 3.2 [2.3] per 1000 catheter days, p=0.009). Access to key decision makers for planning was not significantly associated with CAUTI rates (p=0.804). When the influence of policies and access were controlled for in multivariable analysis, hospital size remained predictive of CAUTI rates; CAUTI rates at hospitals with >500 beds were 1.5 times higher than rates at smaller hospitals (RR=1.55, 95% CI 1.11-2.16). Given the low numbers of ICUs that tracked compliance with CAUTI policies, we were unable to compare CAUTI incidence rates in ICUs with low versus high reported adherence.

Discussion

To our knowledge, only 1 other large study of CAUTI prevention practices in US hospitals has been conducted to date. In 2005, Saint and colleagues surveyed infection control coordinators at acute care Veterans' Affairs (VA) hospitals and at acute care non-VA hospitals with ≥50 beds.[48] Similar to our current study, Saint et al found that there was no single, widely used CAUTI prevention strategy; only 30% of hospitals reported regularly using portable bladder

ultrasound, 14% reported using condom catheters in men, and 9% reported using catheter reminders or stop orders.

In our study, ICUs were more likely to have at least one CAUTI prevention policy in place if their IPC director always had access to key decision makers for planning as opposed to having access most of the time, sometimes, rarely, or never. This may be an indication of a high level of organizational commitment to infection prevention. In a qualitative investigation of why certain hospitals adopt HAI prevention strategies and others do not, Krein and colleagues found that positive organizational context, including leaders' engagement in planning patient safety programs and provision of resources, promoted the adoption of HAI prevention practices at acute care hospitals.[109] The authors noted that "Hospitals with a positive emotional and cultural context, as evidenced by… active and engaged clinical leadership… appear especially conducive for fostering and encouraging internally motivated initiatives."[109 (p1698)] Our findings suggest a low level of organizational commitment to infection control overall, as evidenced by the fact that >42% of ICUs had no HE and only 29% had an electronic surveillance system for tracking HAI.

Our finding that the presence of an HE did not predict policy adoption was in keeping with results of Saint et al.[48] Our finding that teaching status did not predict policy adoption was in contrast to that earlier study, which concluded that hospitals with an approved residency training program were more than 4 times as likely to use urinary catheter reminders or stop-orders than hospitals without residency training programs.[48] The finding that mandatory state reporting of HAI was not significantly associated with CAUTI policy adoption may be explained by the fact that at the time of the study, all but 1 state mandated hospitals to report infections other than CAUTI.[110]

No relationship was identified between CAUTI rates and the existence of CAUTI policies. This is in keeping with the results of concurrent studies which found that simply instituting policies for the prevention of central line-associated bloodstream infection (CLABSI) and ventilator-associated pneumonia (VAP) was not associated with lower infection rates; rather, only when an ICU had ≥95% compliance with CLABSI or VAP prevention policies did corresponding infection rates decrease.[111,112] It is also possible that the negative finding is indicative of mixed causality – that at some hospitals, policy adoption results in low CAUTI rates, while at others policies are adopted in response to high CAUTI rates. If an association between policies and CAUTI rates does exist, it might be difficult to find given the low sensitivity (59%) of CAUTI reporting using the NHSN definitions in place in 2008.[108] Lastly, the number of respondents in our study who provided CAUTI rates and had at least 1 prevention policy in place was low (*n*=65); thus, the study may have been underpowered to find an association.

The finding that larger hospitals have higher CAUTI rates is not surprising. In a HAI prevalence study in 18 acute care hospitals in Switzerland in 1999, Sax, Pittet and colleagues found that the odds ratio for HAI in large hospitals was nearly twice that in small hospitals.[113] However, after controlling for patient case mix factors such as comorbidity, a history of intensive care unit stay, and intubation for more than 24 hours, hospital size was not an independent risk factor for HAI. In our study, hospital size may have been acting as a surrogate for case mix in predicting CAUTI rates.

Our finding that ICUs at larger hospitals were significantly less likely to have adopted at least 1 CAUTI prevention policy is puzzling. We speculate that if larger hospitals have higher

HAI rates overall due to less favorable case mixes, CAUTI prevention may be lost among competing priorities.

Limitations

Some study limitations may have affected our results. First, inclusion criteria led to a sample of hospitals that were larger on average than NHSN and US hospitals.[114] Given our finding that smaller hospitals were more likely to adopt CAUTI prevention policies, this may have biased our results toward the finding of low policy adoption overall. Also, the fact that larger hospitals were over-represented may limit generalizability. Second, since the survey was voluntary, respondents may have differed from non-respondents. However, the similarity of CAUTI rates reported by our sample to that of all NHSN hospitals engenders confidence that selection bias was not at play. Third, self-report bias may have influenced the data; however, that bias should lead to over-reporting of policies to prevent CAUTI. Therefore, the conclusion that there is a notable lack of policies and monitoring would be conservative. Fourth, our survey did not provide information regarding aseptic catheter insertion or maintenance practices; it is possible that hospitals are relying on these strategies to prevent CAUTI. While this may be the case, the fact that nearly two-thirds of the hospitals do not know what their CAUTI rates are implies that reliance on insertion and maintenance practices is an assumption, not a reduction strategy. Fifth, it is possible that policy adoption is not an accurate surrogate for practice adoption. For example, some ICUs that use condom catheters may not have a policy in place specifically promoting their use. Thus, inferences about CAUTI prevention practices must be made with caution. Last, the information garnered in the survey is relatively superficial. Qualitative data are needed to elucidate the complex interplay of internal and external factors

that influence infection control policy and clinical practice. Such a study is underway. Despite these limitations, our findings merit consideration.

Reasons for Low Policy Adoption

The most notable finding is the low prevalence of CAUTI prevention policies. One possible explanation could be a weak evidence base for the recommended strategies. Although many recommendations are consistent across CAUTI prevention guidelines, the studies on which they are based are limited in number, size, and quality.[103] In addition, most CAUTI prevention studies use bacteriuria as the outcome of interest, rather than more clinically relevant measures such as symptomatic CAUTI or urosepsis. In our survey, however, weight of research evidence did not seem to be a factor in the decision to convert CAUTI prevention strategies into policy. Ironically, strategies with weak research evidence (i.e., portable bladder scanners) were codified in policy more often than practices with stronger support in the literature (i.e., catheter reminders or stop orders).[19,103]

Another possible explanation for the low adoption of CAUTI prevention policies is a lack of awareness of current guideline recommendations. This is not likely the case, since newer strategies such as bladder ultrasound to measure urinary retention were more widely adopted than the long-recommended practice of using condom catheters. Results from Saint et al also suggest that lack of awareness was not a factor, since only 3% of U.S. hospitals reported an outdated practice – placing antimicrobial agents in the drainage bag.[48]

A more plausible explanation for the low adoption of CAUTI policies is that preventing these infections is a relatively low priority for hospitals. A comprehensive program to reduce inappropriate catheter use can be effective but resource-intensive.[115] A single CAUTI is not estimated to be as costly as a CLABSI, VAP, or surgical site infection.[13] CAUTI rarely cause

sentinel events.[116] For these reasons, an annual infection control risk assessment would rarely identify CAUTI reduction as a priority. Hospitals may be directing their energies toward what they perceive are more harmful and costly infections.

Negative payment incentives announced at the time of this survey should have effectively elevated CAUTI prevention to priority status. In August 2007, the Centers for Medicare and Medicaid announced that beginning in October 2008 it would no longer reimburse hospitals for costs attributable to CAUTI.[49] Although the specter of non-payment for CAUTI may have induced physicians in at least 1 state to remove catheters earlier,[117] it does not appear to have had a broad effect at the time of this survey. Since the survey, there are indications that the regulation has had a minimal impact on hospitals' bottom line because of problems implementing it. The rule specifies that reimbursement will be withheld for only those CAUTI identified by specific *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. The ICD-9-CM codes "have very limited validity in identifying hospital-acquired CAUTIs, achieving 30% PPV [positive predictive value] at best." [118 (p.368)] Coders must correctly identify the presence of a qualifying UTI, indicate that it was not present on admission, and indicate that a urinary catheter was temporally associated with the UTI in order for payment to be denied. Miscoding at any of the 3 points will result in payment.[119] Meddings et al demonstrated just such miscoding in a study of 80 randomly selected adult discharges with secondary diagnoses of UTI.[120] While a physician-abstractor categorized 35% of the UTIs as hospital-associated CAUTI, none had been coded as such.

State mandates for public reporting of infections also should have elevated CAUTI prevention to priority status, but instead may have inadvertently reduced CAUTI prevention efforts by over-focusing on other HAI. By the end of 2009, 29 states required public reporting of

HAI and 2 allowed confidential reporting to the state.[110,121] Pennsylvania was the only state that specified CAUTI in its legislation.[122]

In the same way, national quality initiatives directed at HAI prevention but slow to target CAUTI specifically may have served to de-prioritize CAUTI infections. The Institute for Healthcare Improvement targeted CLABSI, VAP, and surgical site infection prevention since 2006, but did not add CAUTI as a focus until 2009.[123] Consumers Union's effort to reduce HAI is limited to a comparison of CLABSI rates.[124] The Leapfrog Group's hospital HAI comparisons include CLABSI but not CAUTI rates.[125]

Overall, public policy and quality initiatives in place in 2008 appear to have lacked the strength needed to promote real reduction in CAUTI. As a result, hospitals may not have acted to reduce CAUTI despite the existence of clear practice guidelines. More recent federal quality initiatives may serve to elevate CAUTI prevention to priority status. In 2009, the Department of Health and Human Services added a 5-year goal to reduce CAUTI rates by at least 25% to its Action Plan to Prevent Healthcare-Associated Infections.[99] In 2011 The Joint Commission included the implementation of evidence based practices to prevent CAUTI as one of its 2012 National Patient Safety Goals.[126] This year, the Centers for Medicare and Medicaid enacted public reporting of CAUTI rates through its Hospital Inpatient Quality Reporting Program beginning in 2014 based on data submitted beginning in 2012.[127]

Implications

Results of this study suggest that little attention is focused on CAUTI prevention in ICUs in the US. To address this gap, IPs, HEs, administrators and clinicians should implement policies aimed at limiting unnecessary catheter use and shortening the duration of catheterization at their institutions. Quality improvement organizations that currently direct their efforts toward HAI

prevention in general must take up the cause of CAUTI prevention in particular. Further research is needed to elucidate relationships between adherence to CAUTI prevention recommendations and CAUTI incidence rates.

Table 4.1 Sample Characteristics

	Sample N=415 ICUs % (*n*)	National Healthcare Safety Network[1] N=621 % (*n*)	X^2
Region			
Northeast	41.2 (171)		
South	28.7 (119)		
Midwest	14.9 (62)		
West	15.2 (63)		
Size			
≤200 beds	15.4 (64)	44.0 (273)	$p<0.05$
201-500 beds	54.9 (228)	40.2 (250)	
501-1000 beds	27.0 (112)	15.5 (96)	
>1000 beds	2.7 (11)	0.3 (2)	
Teaching Status*			
Teaching	71.3 (296)	51.7 (321)	$p<0.05$
Non-teaching	28.7 (119)	48.3 (300)	
ICU Type			
Medical teaching	21.0 (87)		
Medical all others	3.9 (16)		
Medical/Surgical teaching	33.5 (139)		
Medical/Surgical all others	20.2 (84)		
Surgical	21.4 (89)		
State Mandatory Reporting			
Yes	63.4 (251)		
No	36.6 (145)		

[1] Edwards et al. National Healthcare Safety Network (NHSN) report, data summary for 2006 through 2007, issued November 2008. *AJIC 2008;* 6:609-626.

*Definition of teaching status is different than that used by NHSN

Table 4.2 CAUTI Prevention Policies and Compliance in ICUs

Does your ICU have a written policy in place to use…?	Policy in Place % (*n*)	Compliance is Tracked % (*n*)	Compliance with Policy % (*n*)		
			Always (≥95%)	Usually, Sometimes or Rarely/Never	Don't Know
1. Clinician use of portable bladder **ultrasound** scanner for determining post void residual	25.9 (106/409)	18.9 (20)	10.0 (2)	15.0 (3)	75.0 (15)
2. **Condom** catheters for men	20.0 (82/410)	8.6 (7)	14.3 (1)	85.7 (6)	0 (0)
3. Urinary catheter reminder or **stop order**	12.4 (51/410)	31.4 (16)	31.3 (5)	56.3 (9)	12.5 (2)
4. **Nurse-initiated** urinary catheter discontinuation	9.5 (39/409)	12.8 (5)	40.0 (2)	20.0 (1)	40.0 (2)
At least 1 policy	42.2 (174/410)	22.4 (39)	15.4 (6)		

Table 4.3 Factors Associated with Having At Least 1 of 4 CAUTI Prevention Policies in Place

	ICU with **at least 1** of 4 CAUTI prevention policies in place *n*=174	ICU with **none** of 4 CAUTI prevention policies in place *n*=234	X^2
Region	**% (*n*)**	**% (*n*)**	
Northeast	39.2 (65)	60.8 (101)	*p*=0.04
South	36.8 (43)	63.2 (74)	
Midwest	50.0 (31)	50.0 (31)	
West	55.6 (35)	44.4 (28)	
Size			
≤200 beds	51.6 (32)	48.4 (30)	*p*=0.09
201-500 beds	44.2 (99)	55.8 (125)	
501-1000 beds	36.9 (41)	63.1 (70)	
>1000 beds	18.2 (2)	81.8 (9)	
Hospital Epidemiologist			
No hospital epidemiologist	44.3 (74)	55.7 (93)	*p*=0.002
Part time or hours not specified	36.2 (72)	63.8 (127)	
Full time	68.8 (22)	31.3 (10)	
Access to Key Organizational Decision Makers for Planning	% (*n*)	% (*n*)	
Never, rarely, sometimes, or most of the time	34.8 (86)	65.2 (161)	*p*<0.001
Always	55.3 (88)	44.7 (71)	
Access to Key Organizational Decision Makers for Problems			
Never, rarely, sometimes or most of the time	35.4 (58)	64.6 (106)	*p*=0.015
Always	47.5 (116)	52.5 (128)	
Electronic Surveillance System			
Yes	50.0 (59)	50.0 (59)	*p*=0.06
No	39.8 (113)	60.2 (171)	

Table 4.4 CAUTI Rates per 1000 Urinary Catheter Days by Unit Type Compared to National Healthcare Safety Network (NHSN)

Unit Type	Sample *n*=172		NHSN 2006-2008[1]	
	n	Pooled mean (median)	*n*	Pooled mean (median)
Medical teaching	32	4.1 (3.3)	53	4.7 (3.8)
Medical all others	5	2.5 (2.8)	59	3.9 (3.0)
Medical/surgical teaching	65	3.3 (3.0)	89	3.4 (3.1)
Medical/surgical all others	34	3.5 (2.4)	≤ 15 beds 235	3.4 (2.1)
			> 15 beds 111	3.1 (2.6)
Surgical	36	4.5 (3.3)	95	4.3 (3.4)

[1]Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control.* Dec 2009;37(10):783-805

Chapter Five: Conclusions

In this dissertation, I examined risk factors for bacteremia secondary to CAB by conducting a systematic review and by evaluating cases and controls in a large clinical and administrative database, and I assessed the prevalence and predictors of catheter policies at US hospitals using data from a national cross-sectional survey. The findings of the three studies indicate that although risk factors for bacteremia secondary to CAB have not been fully elucidated, continued catheter presence may be a factor, and little is being done by US hospitals to reduce unnecessary catheter use.

Results Summary

Our systematic review identified the following potential risk factors for bacteremia secondary to CAB: male sex, immunosuppressant medications, red blood cell transfusion, neutropenia, malignancy, liver disease, and prolonged hospital stay. Antimicrobials were identified as possibly protective. Also, the potential risks posed by underlying urinary tract disease, urinary tract manipulation, CAB pathogen, smoking, and diabetes required further study. The weight and quality of evidence supporting the identified risk factors was weak. To our knowledge, this was the first systematic review on this topic.

Our case-control study confirmed that male sex, immunosuppressant medication, and length of stay prior to CAB are risk factors for bacteremia. Our findings also suggested that younger age, urinary tract procedures, and a catheter remaining in place after CAB may increase the risk for bacteremia, while enterococcal CAB may reduce the risk. Antimicrobials, diabetes, malignancy, and underlying urinary tract disease were not significantly associated with development of bacteremia in our study, clarifying the evidence from earlier studies. We did not test the association of bacteremic CAB with neutropenia, liver disease, smoking, or red blood

cell transfusion. This was the first study to consider the presence of a urinary catheter after CAB as a risk factor for bacteremia.

Our analysis of survey responses found that policies to reduce unnecessary catheter use were uncommon in ICUs in the US. One quarter or fewer had policies in place supporting bladder ultrasound or condom catheter use, and 12% or fewer had policies for catheter reminders or nurse-initiated catheter discontinuation. Only 42% of ICUs had adopted at least one policy, and those that did were twice as likely to be in smaller hospitals or in hospitals where the infection prevention director had unlimited access to key decision makers for planning. We did not find an association between having at least one catheter policy in place and CAUTI rates.

Strengths and Limitations

This dissertation has two major strengths; results of the studies are highly generalizable and the threats to internal validity were minimized within the constraints of the observational designs. The case control study sampled a large tertiary care center as well as a small community hospital, and the cross-sectional survey included a heterogeneous sample of ICUs in hospitals of different sizes from all regions of the US, yielding strong external validity for both studies.

Bias and confounding were minimized as far as possible. Selection and information bias were minimized in the systematic review by adhering to a carefully designed protocol, using the expertise of a medical librarian for the search, and using two independent reviewers for sample selection, data extraction, and appraisal. Sampling bias was avoided in the matched case control study by randomly sampling controls from among all patients with CAB admitted within +/- 30 days. Also, the possibility of statistical bias was minimized by sampling a large number of cases and controls, enabling us to detect small differences in risk of bacteremia. Finally, in both the

case-control and cross-sectional survey studies we minimized the potential for confounding by examining numerous predictor variables and using multivariable regression analyses.

This dissertation also has some limitations. First, because case control and cross-sectional designs were used, we cannot infer that any of the predictor variables causes the outcome; i.e., we cannot infer that any of the identified risk factors causes bacteremia or that any of the hospital characteristics results in policy adoption. Second, the use of existing electronic and self-reported data limited the quality of data and the variables available. In the case control study, electronic data such as ICD-9 codes may have been inaccurate, clinical cultures may have led to misclassification of cases or controls, and unavailability of data (e.g., transfusion history) may have resulted in confounding. Similarly in the survey, participants may have responded to questions inaccurately in order to present themselves in a better light, and some potentially useful data (e.g., catheter utilization ratios as an outcome) were not available. In the systematic review, there were too few studies and the risk factors were too dissimilar to permit a quantitative synthesis of results. Third, selection bias may have affected results. In the systematic review, exclusion of grey literature and non-English language studies may have led to studies being missed. The survey was vulnerable to self-selection bias because it was voluntary, thus participating hospitals may have differed from non-participating hospitals in ways that affected adoption of catheter policies.

Implications

Despite these limitations, the findings of this dissertation have direct implications for future research, practice, and policy.

Implications for Future Research

Risk factors for bacteremia after CAB have not been sufficiently elucidated to warrant an interventional study. In fact, with the exception of urinary catheter use, none of the risk factors lends itself to intervention. Also, following patients with CAB prospectively would not be feasible given the rarity of subsequent bacteremia. However, another case control study that included some of the variables we were not able to factor in, such as indication for catheterization, the presence or absence of urinary tract symptoms, and the indication and appropriateness of antimicrobials prescribed would be worthwhile. Development and testing of a risk assessment tool would also be worthwhile. In addition, data comparing the incidence of urinary tract-related bacteremia in patients with urethral catheters versus condom catheters and suprapubic catheters is needed. Also, our findings beg the question of whether changing a urethral catheter rather than removing it altogether might decrease or increase the risk for subsequent bacteremia. Although secondary bacteremia is a rare outcome, it might be assessed prospectively as part of a larger study examining multiple outcomes such as recurrent CAB or antimicrobial use.

Given the low levels of adoption of catheter reduction policies, the questions of why policies have not been adopted and what interventions might improve uptake are ripe for research. Qualitative explorations and implementation science studies are needed to answer these questions.

Implications for Practice

The findings of this dissertation are useful for informing clinical practice. Certain patients may be considered at high risk for bacteremia secondary to CAB, as noted above. These patients should have their catheters removed as soon as possible, or replaced with an alternative such as

intermittent catheterization or condom drainage in cooperative patients without outlet obstruction. Suprapubic catheterization could be considered for short-term bladder drainage in adults with multiple risk factors. High risk patients could be identified in automatic stop orders and nurse-driven protocols for catheter removal.

In addition, clinicians can use the results of these studies to inform their decision regarding whether or not to treat CAB in a patient who is unable to report the presence or absence of symptoms. For example, patients with enterococcal CAB could be considered at lower risk for bacteremia than those with other causative organisms.

Policy Implications

The findings also have policy implications at the local and national level. Clinicians and hospital administrators should work to implement policies aimed at limiting unnecessary catheter use and shortening the duration of catheterization at their hospitals. Doing so would have the added benefit of reducing non-infectious adverse outcomes of catheterization such as trauma, pain, restriction of movement, and embarrassment.[128-130]

At the national level, a complete picture of the burden of bacteremia secondary to nosocomial CAB is needed. This could be accomplished through the National Healthcare Safety Network (NHSN). Currently, hospitals must report symptomatic CAUTI and asymptomatic bacteremic CAB in adult and pediatric ICUs and medical and surgical wards to NHSN in order to fulfill the Centers for Medicare & Medicaid's Hospital Inpatient Quality Reporting requirements. The incidence of both of these types of infections are published annually. However, bacteremia secondary to symptomatic CAUTI is not included, even though the NHSN reporting form for symptomatic CAUTI includes a check box for secondary bacteremia. Thus,

epidemiologic data for the total incidence of bacteremia secondary to asymptomatic and symptomatic urinary tract infection is available but is not published.

Finally, the risks for bacteremia secondary to CAB identified in this dissertation could be used to create a risk-adjustment model for asymptomatic bacteremic CAB rates which are currently publicly reported through NHSN as part of CAUTI reporting.[131] For example, given that males are at increased risk, adjusting for the proportion of male patients would produce less biased estimates when VA hospitals, which have high proportions of male patients, are compared to other hospitals.

In summary, this dissertation has identified risk factors for bacteremia secondary to CAB and has determined the prevalence and predictors of adoption of catheter reduction policies at US hospitals. This information may be used by clinicians, researchers, and policy makers to advance the delivery of care and improve patient outcomes.

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