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The reliability and diagnostic validity of clinical manifestations of catheter-associated urinary tract infection in hospitalized adults: a pilot study

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THE RELIABILITY AND DIAGNOSTIC VALIDITY OF CLINCAL MANIFESTATIONS OF CATHETER-ASSOCIATED URINARY TRACT INFECTION IN HOSPITALIZED ADULTS: A PILOT STUDY

by

Thomas J. Blodgett

An Abstract

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ABSTRACT

Catheter-associated urinary tract infection is a common clinical condition among hospitalized patients with numerous health and economic implications. With judicious use of indwelling urinary catheters, along with strict adherence to basic infection prevention measures, such as hand hygiene and aseptic technique during catheter insertion, these infections are most often preventable. However, these devices continue to be used inappropriately or unnecessarily, which has led the Center for Medicare and Medicaid Services (CMS), the Centers for Disease Control and Prevention (CDC), and numerous infectious disease professional societies to focus attention on how these infections can be diagnosed, prevented, and managed. Despite these efforts, consensus on how best to identify cases of CAUTI has been elusive.

Perhaps the most widely used guidelines for the diagnosis, prevention, and treatment of CAUTI are those published in 2010 in the American Journal of Infection Control by Hooton and colleagues. These authors are very clear that CAUTI is a problem if, and only if, it is associated with clinical manifestations; the presence of urinary microorganisms alone is not a clear indication for antimicrobial therapy. Moreover, these authors provide a list of accepted clinical manifestations of CAUTI, which are substantially different from those in previous guidelines. Among others, the manifestations listed include: fever, suprapubic tenderness, flank tenderness, and delirium. However, these are supported by expert opinion only, and neither their diagnostic validity nor their inter-rater reliability have been reported in the literature.

The purpose of this study was to test the feasibility of methods to examine the diagnostic validity and inter-rater reliability of fever, suprapubic tenderness, flank

tenderness, and delirium in hospitalized adult with an indwelling urinary catheter. Briefly, these clinical manifestations were compared against three diagnostic criteria for CAUTI based on microbiologic and molecular methods, and their inter-rater reliability was examined using assessments conducted by three advanced practice nurses.

Because significant microbial growth was only present in two urine samples, the diagnostic validity of these manifestations could not be established. However, it was possible to examine the inter-rater reliability of these manifestations. To summarize these findings, the nurse raters were in perfect agreement with the identification of fever, moderate agreement with the identification of delirium, and fair agreement with the identification of suprapubic tenderness and flank tenderness. With the exception of flank tenderness, these findings are statistically significant, and they provide evidence that nurses can consistently identify the presence and absence of fever, suprapubic tenderness, and delirium in hospitalized patients with indwelling urinary catheters. This study provided preliminary findings that support the need for further investigation of the diagnostic validity of clinical manifestations of CAUTI. However, this study had several limitations, and further research is necessary to understand the overall clinical utility and value of these manifestations in terms of patient outcomes and cost.

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CERTIFICATE OF APPROVAL

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PH.D. THESIS

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To Nikki, Colin, and Drew

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CHAPTER I

INTRODUCTION

Background

Catheter-associated urinary tract infection (CAUTI) among hospitalized adults and older adults is a common, costly, and potentially life-threatening iatrogenic infection. Hospital-acquired UTI, which encompasses CAUTI and other types of UTI that occur during hospitalization, account for 40% of all nosocomial infections in United States hospitals each year (Tambyah, Knasinski, & Maki, 2002). Furthermore, nearly 30% of catheterized patients will go on to develop symptomatic bacteriuria, or CAUTI (Warren, 2001), which requires aggressive antimicrobial pharmacotherapy and discontinuation of the indwelling urinary catheter.

Gram-negative bacteremia and urosepsis are among the most detrimental consequences of CAUTI. Nearly 18% of patients with urinary tract-related bacteremia have hospital-acquired UTI, and death from urosepsis is more likely in patients with CAUTI than community-acquired UTI (C. I. Kang et al., 2011). Moreover, antimicrobial resistance is an increasingly common complication of CAUTI (Ko et al., 2008), with resistance rates for ciprofloxacin up to 100% and for trimethoprim-sulfamethoxazole up to 70% in patients hospitalized for urologic surgery (Milan & Ivan, 2009).

Catheter-associated UTI is also of significant economic concern for hospital patients, third-party payers, and health care systems. Recent changes in prospective payment regulations from the Center for Medicare and Medicaid Studies (CMS) state that treatment for certain iatrogenic complications, including CAUTI, were not covered for their beneficiaries as of October 1, 2008 (CMS unveils proposed list of 'no-payment'

conditions.2007; Vesely, 2007). Moreover, many private insurers have begun to deny coverage for iatrogenic complications such as CAUTI (Kurtzman & Buerhaus, 2008). While CAUTI increased the cost of hospitalization by only $500 to $1,000 per episode, complications from CAUTI are substantially more expensive. Urosepsis costs up to $21,000 per episode in hospitalized patients over the age of 65. Moreover, delirium, for which both urinary catheterization and UTI are known to be independent risk factors in hospitalized older patients, increases the overall cost of hospitalization by 31%. Other complications of CAUTI include: urinary tract stone formation, urinary incontinence, bladder outflow obstruction, and antimicrobial resistance. Clearly, CAUTI represents a common hospital-acquired condition with potentially devastating clinical and economic consequences.

Nearly 25% of hospital patients will undergo urinary catheterization during their hospitalization (S. Saint, 2000b), and the challenges of CAUTI prevention in these patients can be difficult to overcome. Although necessary in many acute care situations, inappropriate catheter use occurs in up to half of catheterized patients (Gokula, Hickner, & Smith, 2004). Strategies to guide clinicians in prescribing and discontinuing catheter use have produced mixed, although promising, results. However, the duration of catheterization remains the most significant factor in predicting CAUTI (Beaujean et al., 1997), and each day of catheterization increases the risk of CAUTI by 3% to 10% (S. Saint, Lipsky, & Goold, 2002). Left undiagnosed and untreated, CAUTI increases the risk for complications and ultimately decreases the efficiency of health care delivery.

Despite the importance of detecting and treating CAUTI in a timely manner, how to identify patients with true infection remains unclear. When indwelling urinary catheter

use is warranted, the overidentification of CAUTI may result in the administration of unnecessary antimicrobial medications, premature removal of the catheter, and complications related to the underlying reason for catheter insertion (e.g. fluid balance monitoring). Conversely, underidentification of CAUTI may result in prolonged urinary catheter use, urosepsis, and death.

In order to correctly identify patients with CAUTI, and thus prevent complications associated with potential overtreatment or undertreatment, two major diagnostic criteria must be met: First, the urine must contain a significant concentration of uropathogenic microorganisms. Second, the infected host must demonstrate evidence of an inflammatory response within the urinary tract in the form of inflammatory biomarkers or clinical manifestations. The diagnostic validity of laboratory-based methods to detect both significant bacteriuria and biomarkers of urinary tract inflammation has been examined in humans and animal models. However, the reliability and diagnostic validity of clinical manifestations of a host inflammatory response to uropathogens remains unclear, even though clinical manifestations are more readily accessible than laboratory markers of inflammation.

Traditionally, the quantitative urine culture has been used to identify the presence or absence of significant bacteriuria. This test requires approximately 24 hours to produce meaningful information about the concentration of bacteria in urine. Although several cut points have been used to define the lower limit of this significant bacterial concentration, most CAUTI diagnostic guidelines choose either 1,000 colony-forming units per milliliter (cfu/mL) of urine or 100,000 cfu/mL. Although the quantitative urine culture has gained widespread support as the “gold standard” in CAUTI diagnosis, regardless of

the cut point used, this test has several important limitations. First, because systemic complications of CAUTI generally develop as the concentration of uropathogens increases, the quantitative urine culture may not provide meaningful results in time to initiate antimicrobial therapy before the onset of urosepsis. Second, the quantitative urine culture does not provide information about the virulence of the isolated microorganisms, and therefore cannot differentiate CAUTI from catheter-associated asymptomatic bacteriuria, which occurs when a large number of avirulent reproducing microorganisms is present in the urinary tract without inducing a host response or tissue damage.

The inability to differentiate significant bacteriuria with virulent microorganisms from asymptomatic bacteriuria with avirulent microorganisms is a major limitation of quantitative urine cultures. Using qualitative urine cultures and biochemical analyses (e.g. lactose fermentation), the species of an isolated microorganism can usually be identified. However, because the expression of virulence factors can vary within a species, particularly among common uropathogens such as *Escherichia coli*, identifying a microorganism at the species level may be inadequate to predict its potential to cause CAUTI.

Phylogenetic analyses have been used to classify bacterial species into groups based on common genetic features that are directly or indirectly related to the capacity to cause disease. For example, *E. coli* has been classified into four major phylogenetic groups: A, B1, B2, and D; those in groups A and B1 are extremely unlikely to cause infection in humans, whereas those in groups B2 and D are more likely to do so.

Clermont and colleagues (Clermont, Bonacorsi, & Bingen, 2000) have developed a two-step decision-tree model that uses polymerase chain reaction (PCR) to identify two

genes (*chuA* and *yjaA*) and one gene fragment (TspE4.C2) to classify extraintestinal *E. coli* isolates into four phylogenetic groups with 80% to 99% accuracy. These genes and gene fragments, although not necessarily virulence factors themselves, have been phylogenetically associated with myriad virulence characteristics, including: hemolysis and tissue destruction, tissue adhesion, antimicrobial resistance, and iron-sequestration. The combination of virulence characteristics that an uropathogen expresses ultimately determines the potential to elicit a host inflammatory response. Therefore, methods to identify virulence genes or phylogenetic group membership provide a more robust and complete measure of CAUTI than quantitative urine cultures.

Similar procedures to classify non-*E. coli* isolates by phylogenetic group have been developed. However, since *E. coli* is the most common uropathogenic strain associated with CAUTI, identifying the clinical utility of phylogenetic classification of this species may be an appropriate first step in exploring this strategy as an alternative measure for CAUTI in research. The major limitation of these methods is that they require substantial technological, human, and financial resources that exceed the current infrastructure of many clinical laboratories.

For clinical practice, diagnostic guidelines for CAUTI endorse using a combination of laboratory evidence of significant bacteriuria (i.e. quantitative urine cultures) and the following clinical manifestations: fever, suprapubic tenderness, flank tenderness, and delirium. These manifestations are believed to be independent of the catheter itself and direct indicative of pathogen-induced tissue damage and host inflammatory response. However, the association between the expression of CAUTI manifestations and the concentration of uropathogens is unknown. Their presence may

indicate either true infection or tissue irritation from the catheter materials. Conversely, their absence may indicate either avirulent microorganisms (i.e. asymptomatic bacteriuria) or a blunted host inflammatory response to virulent microorganisms. Examining the expression of clinical manifestations of CAUTI in assocation with the phylogenetic grouping of microorganisms present in significant numbers in the urine provides an alternative method to determine the diagnostic validity of clinical manifestations. If clinical manifestations of CAUTI are strongly associated with the phyogenetic grop of an uropathogen, then clinical manifestations can be considered useful indicators of the potential for CAUTI and its numerous and costly consequences. The problem is that the diagnostic validity of the clinical manifestations of CAUTI has not been examind in association with any laboratory measure of CAUTI, including quantitative urine cultures or phylogenetic groups. Compounding the lack of knowledge regarding diagnostic validity, the reliability with which clinical manifestations of CAUTI are identified among clinicians has never been addressed.

Significance to Nursing

In the acute care setting, nurses provide routine assessment and management of patients with indwelling urinary catheters. Nurses are responsible for the sterile insertion, appropriate function, and timely removal of the indwelling urinary catheter. They are also responsible for the identification of clinical manifestations of CAUTI. Unfortunately, procedures for assessing the clinical manifestations of CAUTI have only been vaguely delineated and/or operationalized for clinical practice. In order for nurses to confidently and consistently identify patients with clinical manifestations of CAUTI, a structured method for assessing them needs to be developed and tested. Development of a structured

method would improve the ability of nurses to identify, plan and implement interventions to prevent the complications associated with undiagnosed infection.

While CAUTI is associated with numerous clinical complications, including urosepsis, delirium, and death, there are also economic consequences of undiagnosed and untreated CAUTI. For example, patients with urosepsis may require aggressive antimicrobial therapy, vasoactive medications, and mechanical ventilation. This level of care requires specialized equipment, space, supplies, nursing knowledge, and nursing skills. Furthermore, the patient with delirium requires continuous monitoring for unpredictable and impulsive behaviors, which lead to falls, traumatic discontinuation of indwelling urinary catheters and other medical devices, and other injuries. Both urosepsis and delirium increase the duration and cost of hospitalization and these potential complications of CAUTI place an enormous economic burden on the health care system. Therefore, timely identification of patients with infection through assessment of CAUTI clinical manfestations has the potential to conserve health care resources.

Research aimed at examining the reliability and diagnostic validity of the clinical manifestations of CAUTI may help nurses and other clinicians make confident and consistent decisions about the identification of patients with CAUTI. With evidence about their reliability and diagnostic validity, guidelines focusing on the clinical diagnosis and management of CAUTI can be revised to reflect the evidence-based role of CAUTI clinical manifestations. Areas for guideline revision may include routine CAUTI surveillance, case identification, and strategies to improve the efficiency of laboratory-based CAUTI diagnosis.

Purpose

The purpose of this study was to test the feasibility of methods to determine the diagnostic validity of clinical manifestations of CAUTI (i.e. suprapubic tenderness, flank tenderness, fever, and delirium) to detect CAUTI defined by three different laboratory measures of CAUTI (i.e. quantitative urine cultures greater than or equal to 10^5, quantitative urine cultures greater than or equal to 10^3 cfu/mL and a concentration of uropathogenic *E. coli* greater than or equal to 10^3) in a sample of hospitalized adults with short-term indwelling urinary catheters.

Research Questions

1. What is the sensitivity, specificity, PV+, and PV- of each of the clinical manifestations of CAUTI among a sample of hospitalized adults with a short-term indwelling urinary catheter as compared to a cut value of greater than, or equal to, 10^5 cfu/mL of any microorganism (reference standard)?
2. What is the sensitivity, specificity, PV+, and PV- of each of the clinical manifestations of CAUTI among a sample of hospitalized adults with a short-term indwelling urinary catheter as compared to a cut value of greater than, or equal to, 10^3 cfu/mL of any microorganism (reference standard)?
3. What is the sensitivity, specificity, PV+, and PV- of each of the clinical manifestations of CAUTI among a sample of hospitalized adults with a short-term indwelling urinary catheter as compared to a cut value of greater than, or equal to, 10^3 cfu/mL of uropathogenic *E. coli* (reference standard)?
4. What is the inter-rater reliability of each of the CAUTI manifestations in hospitalized adults with a short-term indwelling urinary catheter?

5. What combination of demographic factors, clinical factors, and clinical manifestations of CAUTI provides the composite score with the highest diagnostic validity for CAUTI in a sample of hospitalized adults with a short-term indwelling urinary catheter?

Conceptual Definition of Terms

Short-Term Indwelling Urinary Catheter

An indwelling urinary catheter is a hollow, flexible tube that is inserted transurethrally into the bladder to provide continuous, usually gravity-dependent, urine drainage for a period of time greater than that required to initially evacuate the bladder contents. A short-term indwelling urinary catheter is one that is used for a specific clinical purpose that is expected to resolve during or shortly after hospitalization.

Catheter-Associated Urinary Tract Infection

Catheter-associated urinary tract infection is a type of UTI in which the insertion of an indwelling urinary catheter precedes the onset of infection. An infection is a life-threatening, although preventable and treatable disease state in which an actively replicating pathogenic microorganism involves a host organism, damages host tissue, and triggers a localized and/or systemic host immune response, which may generate clinically evident manifestations of host tissue destruction. A urinary tract infection is an infection that occurs in the urothelial lining of urinary tract tissues, including the urethra, bladder, and renal pelvis.

Clinical Manifestations of Catheter-Associated Urinary Tract Infections

Clinical manifestations of CAUTI are assessment findings resulting from the initiation and progression of a host inflammatory response to uropathogens that are

detectable by direct observation, use of specialized medical equipment, or patient report. Clinical manifestations specific to CAUTI include fever, suprapubic tenderness, flank tenderness, and delirium.

CHAPTER II

REVIEW OF THE LITERATURE

Overview

In this chapter, current diagnostic criteria for catheter-associated urinary tract infection (CAUTI) will be examined for conceptual validity in hospitalized older adults. Because these criteria are based on those for asymptomatic bacteriuria and urinary tract infections (UTI) in the absence of urinary catheterization, the first section of this chapter will synthesize the current literature about the pathophysiologic mechanisms and clinical features of these conditions in older adults. The second section of this chapter will address the biologic effects of transurethral bladder catheterization on the pathophysiology and clinical features of UTI and asymptomatic bacteriuria. Finally, the third section of this chapter will propose a conceptual model to illustrate the relationships between the pathophysiologic mechanisms and clinical features of CAUTI in hospitalized older adults.

Bacteriuric Conditions in Hospitalized Adults

Although the urinary tract is generally considered a sterile environment, bacteriuria is a common diagnostic finding in hospitalized adults. Whether or not clinical signs and symptoms of infection occur depends upon the microbiologic and molecular interactions between the host and the microorganisms within the urinary tract. Bacterial virulence factors and host defense mechanisms determine the nature of these interactions, the extent of tissue damage within the host, and the ultimate consequences of the host-microorganism dyad. This section will describe two major classifications of bacteriuric

conditions in hospitalized adults, which differ primarily in their potential to increase morbidity and mortality: asymptomatic bacteriuria and UTI.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is a benign condition in which an actively replicating avirulent bacterial strain colonizes the host urinary tract in the absence of clinical signs and symptoms that would otherwise indicate a host inflammatory or immune response to pathogen-induced uroepithelial tissue damage.

Prevalence and Outcomes

Estimates of the prevalence of asymptomatic bacteriuria range from 19% to 50% in women over the age of 65, and from 7.9% to 20% in men over the age of 65 (Rodhe, Molstad, Englund, & Svardsudd, 2006; Rodhe et al., 2008) [2,6]. Risk factors for asymptomatic bacteriuria are commonly associated with aging. These include: decreased estrogen, increased vaginal pH, and decreased bacteriostatic activity of prostatic secretions (Boyko, Fihn, Scholes, Abraham, & Monsey, 2005; Moore, Jackson, Boyko, Scholes, & Fihn, 2008; Wagenlehner, Naber, & Weidner, 2005).

By definition, asymptomatic bacteriuria is not associated with clinical signs or symptoms of UTI. In fact, fewer than half of hospitalized older adults with culture-confirmed UTI demonstrate urinary tract manifestations (Woodford & George, 2009). Furthermore, this condition is not associated with increased risk for mortality in most older adult populations (Abrutyn et al., 1994; L. E. Nicolle, Bjornson, Harding, & MacDonell, 1983; L. E. Nicolle, Mayhew, & Bryan, 1987; Ouslander et al., 1995). Because this condition is relatively benign, and inappropriate antimicrobial therapy results in antimicrobial resistance among microorganisms, current guidelines for the

management of asymptomatic bacteriuria recommend against routine screening and treatment for this condition in the elderly (L. Nicolle et al., 2005).

Asymptomatic bacteriuria has been associated with an increased risk for developing UTI. Hazelett and colleagues (Hazelett, Tsai, Gareri, & Allen, 2006) found that 69% of hospitalized older adults diagnosed with CAUTI by discharge had significant asymptomatic bacteriuria prior to hospitalization or catheterization. Furthermore, Ribera and colleagues (Ribera et al., 2006) found that patients with diabetes and asymptomatic bacteriuria were more likely to develop UTI than diabetic patients without asymptomatic bacteriuria. The exact mechanism by which asymptomatic bacteriuria leads to UTI is unclear. Two pathways have been proposed.

One hypothesis is that non-pathogenic bacteria become pathogenic bacteria through the transfer of genetic material from a small inoculum of pathogenic bacteria from an environmental source. Avirulent bacteria can receive genetic material from nearby pathogenic strains and become pathogens themselves. Using transduction (use of bacteriophages to transport genetic material), conjugation (use of a sex pilus or other adhesin molecule to transport genetic material), or other mechanisms, virulence genes can be passed from one microorganism to another (Gal-Mor & Finlay, 2006; Kado, 2009). Bacteria in close physical contact will often share genes that offer some evolutionary advantage. For example, it is often advantageous for bacteria in aqueous environments, such as the urinary bladder, to utilize adhesins to withstand the mechanical force of voiding. However, adhesins such as P fimbriae trigger a strong host inflammatory response (Wullt et al., 2001; Wullt, 2003), and bacteria possessing these

molecules would be considered pathogenic rather than avirulent since the host would display manifestations of infection.

The second hypothesis is that after the introduction of pathogenic bacteria into the bladder, the pathogenic bacteria multiply in number and simply overwhelm the avirulent strain (Ferrieres, Hancock, & Klemm, 2007), which could not survive the evolutionary pressure within the bladder. Regardless of the mechanism, it appears that patients can experience a change in their clinical status from being asymptomatically colonized with commensal bacteria to becoming infected when uropathogens invade or develop within the bladder. Therefore, asymptomatic bacteriuria may be a risk factor for UTI and CAUTI.

In addition to the relationship between pre-existing asymptomatic bacteriuria and the development of UTI, the presence of asymptomatic bacteriuria can itself complicate the diagnosis of UTI and CAUTI (Woodford & George, 2009). While the primary diagnostic criterion for all three of these conditions is quantification of bacteria in the urine, this does not take into account the virulence of isolated strains. Patients who are colonized with a significant concentration of avirulent bacteria are unlikely to present with manifestations of infection, whereas patients with the same concentration of uropathogens is likely to develop manifestations of UTI. Although the presence of localized urinary tract symptoms is an important criterion for the diagnosis of UTI and CAUTI (Hooton et al., 2010), a lack of consistency in techniques used to assess these clinical signs and symptoms interferes with the reliable and accurate diagnosis of these conditions (Gau et al., 2009; Juthani-Mehta et al., 2007). Therefore, definitions of UTI and CAUTI that rely on quantitative microbiological analyses alone, without the

differentiation between virulent and avirulent strains, or that do not explicate the techniques to be used during the assessment of localized UTI manifestations, may lead to an inaccurate conclusion about the presence or absence of UTI or CAUTI.

Pathophysiology

While the urinary tract is normally sterile, the presence of certain strains of microorganisms in the urinary tract may not be harmful, and in some cases may even be beneficial (Hancock, Seshasayee, Ussery, Luscombe, & Klemm, 2008; Hutt, Shchepetova, Loivukene, Kullisaar, & Mikelsaar, 2006; Trautner, Hull, Thornby, & Darouiche, 2007). Alternatively, bacteria may possess an assortment of virulence factors that determine the capacity for each genetic strain to cause tissue damage within a host, which leads to the development of clinically evident signs and symptoms of infection. Bacteria that are present in the urine of patients with asymptomatic bacteriuria have attenuated or absent expression of these virulence factors, resulting in an apparent absence of clinical disease (Mabbett et al., 2009; Zdziarski, Svanborg, Wullt, Hacker, & Dobrindt, 2008).

Because avirulent strains of urinary bacteria do not express an adequate supply of virulence factors, they do not generally invade or destroy host uroepithelial tissue (Mabbett et al., 2009). Furthermore, the host immune system does not readily detect these strains because they do not express key antigenic structures, which are found on the structures that contribute to the virulence of that strain (Rodhe, Lofgren, Strindhall, Matussek, & Molstad, 2009; Zdziarski et al., 2008). Finally, the presence of a colony of avirulent bacteria in the urine limits the resources available for the establishment of more virulent strains of bacteria within the urinary milieu (Roos, Ulett, Schembri, & Klemm,

2006). In general, asymptomatic bacteriuria does not affect the health of host uroepithelial cells and, therefore, does not contribute to poor clinical outcomes in the host.

Summary

In summary, asymptomatic bacteriuria is very common among older adults and may be a risk factor for the development of UTI and CAUTI. Moreover, its presence may complicate the accurate diagnosis of UTI, especially in older adults.

Urinary Tract Infection

An infection is a life-threatening, although preventable and treatable, disease state in which an actively replicating pathogenic microorganism invades a host organism, damages host tissue, and triggers a localized and/or systemic host immune response, which may generate clinically evident signs and symptoms of tissue destruction. In contrast to asymptomatic bacteriuria, UTI is a potentially life-threatening condition that is associated with host tissue damage resulting from bacterial virulence factors and mediators of the host immune response to infection (Lane & Mobley, 2007; Ong, Beatson, McEwan, & Schembri, 2009; Selvarangan et al., 2004; Wullt, 2003). There are three major types of UTI: pyelonephritis, cystitis, and urethritis. These infections are isolated to the kidney, bladder, and urethra, respectively.

Prevalence and Outcomes

Among adults, UTI is the most common type of infectious disease (Edwards et al., 2007; Humphreys et al., 2008; Laupland, Ross, Pitout, Church, & Gregson, 2007). Almost half of all women and 13% of all men in the United States will have at least one episode of UTI during their lifetime, and the frequency of UTI increases

disproportionately with age in both genders (Foxman, 2002; Griebling, 2005a; Griebling, 2005b; Nys, van Merode, Bartelds, & Stobberingh, 2006). Direct and indirect costs of UTI among women and men in 2000 were approximately $2.5 billion and $1 billion, respectively, with a total cost of $315 billion (Foxman, 2002; D. C. Miller, Saigal, & Litwin, 2009).

Pathophysiology

With the exception of the distal urethra, the urinary tract is a sterile environment (Zasloff, 2007). Several host defense mechanisms prevent microorganisms from ascending to the proximal urethra, bladder, ureters, and kidneys. These include the urinary sphincters, alpha- and beta-defensins, and the outward flow of urine (Ali, Townes, Hall, & Pickard, 2009; Rodhe et al., 2009). However, in patients with UTI these mechanisms may be dysfunctional or absent, or the concentration or virulence of uropathogens in and around the urethral opening may be sufficiently high to overwhelm these mechanisms (Moreno et al., 2008). Moreover, uropathogens may express a redundancy of adhesins, invasins, and other virulence factors that aid in their capacity to ascend the urinary tract (Bergsten, Wullt, & Svanborg, 2005; Lane & Mobley, 2007; Selvarangan et al., 2004; Snyder et al., 2005). Upon gaining entry into this sterile environment, uropathogens adhere tightly to the uroepithelium and multiply rapidly along the uroepithelial lumen (Selvarangan et al., 2004; Snyder et al., 2005). The host immune response to these pathogenic microorganisms, which includes the inflammatory response, is triggered when lipopolysaccharide and other pathogen-associated molecular patterns (PAMPs) interact with Toll-like receptors (TLR) on the host uroepithelium (Mossman et al., 2008). Mediators of the host immune response, such as cytokines and bradykinins,

along with uropathogenic toxin molecules, destroy host urinary tract tissues and interact with the central nervous system to produce clinical manifestations of infection (Mills, Meysick, & O'Brien, 2000; Y. C. Smith, Rasmussen, Grande, Conran, & O'Brien, 2008; Svanborg et al., 2001). In general, patients with UTI experience pain referable to the urinary tract [1,3-5] (Ducharme, Neilson, & Ginn, 2007; Medina-Bombardo, Segui-Diaz, Roca-Fusalba, Llobera, & dysuria team, 2003; Rudick et al., 2010; Woodford & George, 2009), voiding difficulties, and fever. This section will provide specific details about pathogen and host physiology that interact to produce clinical evidence of UTI.

Microbiologic Characteristics of UTI

Most cases of UTI are associated with uropathogenic strains of *Escherichia coli*, which often originate within the host's intestinal tract and migrate *vis a vis* the perineum to the urethral opening, where they ascend to the bladder and other urinary tract structures (Monane et al., 1995; Moreno et al., 2006; Moreno et al., 2008; Nys et al., 2006). While several other microbial species may be responsible for UTI, *E. coli* is present in the urine of approximately 74% of ambulatory UTI, 66% of cases of UTI diagnosed during the first 2 days of hospitalization, and 47% of cases involving residents living in nursing homes (Laupland et al., 2007). Three major microbiologic variables affect the clinical course and outcome of UTI: [RW.ERROR - Unable to parse:] uropathogen concentration, virulence factor expression, and biofilm formation. These characteristics are described below.

Uropathogen Concentration

Uropathogen concentration reflects the fact that bacteria that have gained entry to the urinary tract are actively replicating. Higher concentrations of planktonic, or free-

floating, bacteria in the urine are more likely to cause UTI-related complications, such as acute pyelonephritis and urosepsis, than lower concentrations of uropathogens (Kass, 1956; Kunin, White, & Hua, 1993). The cut-off value for "significant" bacteriuria, which is the concentration above which a patient's risk for death from bacteriuria increases significantly, has been established at 100,000 colony-forming units per milliliter of urine (10^5 cfu/mL) (Hooton et al., 2010; Kass, 1956). However, there is some debate in the literature on the appropriateness of this value in particular populations, including the elderly and those with indwelling urinary catheters (Heinamaki, Haavisto, Hakulinen, Mattila, & Rajala, 1986; Platt, 1983; Stamm, 1988; Stamm, 1992; Tambyah & Maki, 2000b). Some authors assert that older adults, especially those with several comorbid conditions and risk factors for UTI, have increased mortality at a much lower concentration of uropathogens (e.g. 10^3 cfu/mL) (Heinamaki et al., 1986; Nordenstam, Brandberg, Oden, Svanborg Eden, & Svanborg, 1986). Moreover, older adults who present with atypical manifestations of infection, such as delirium and functional decline, will go undiagnosed and may develop life-threatening complications if the clinician delays, or fails to perform, diagnostic testing for UTI (Lim, Doshi, Castasus, Lim, & Mamun, 2006; Midthun, 2004; Woodford & George, 2009). Therefore, a lower cut-off value for "significant" bacteriuria is recommended in high-risk elderly populations.

Virulence Factor Expression

Each uropathogen has a unique capacity to cause disease in the human urinary tract, which is referred to as its pathogenicity. Virulence factors are physical structures or biochemical properties that determine the pathogenicity of a microorganism (Relman & Falkow, 2005). The genetic material that encodes these virulence factors is found on

pathogenicity islands and islets within the chromosomal DNA of the uropathogen, as well as extra-chromosomal plasmids (Gal-Mor & Finlay, 2006; Hacker, Blum-Oehler, Hochhut, & Dobrindt, 2003; Oelschlaeger, Dobrindt, & Hacker, 2002). Phylogenetic analyses have demonstrated that *E. coli* can be categorized into four major phylogenetic groups, each with differing virulence characteristics: A, B1, B2, and D (Herzer, Inouye, Inouye, & Whittam, 1990; Selander, Musser, Caugant, Gilmour, & Whittam, 1987). Most virulent *E. coli* strains are members of groups B2 or D, while avirulent strains are members of groups A or B1 (Bingen-Bidois et al., 2002; Ghenghesh et al., 2009; Hancock, Nielsen, Krag, Engberg, & Klemm, 2009; Johnson et al., 2005; Moreno et al., 2009). Johnson and colleagues (2006) found that wild-type mice were more likely to die from *E. coli* UTI when the uropathogen was identified as being from group B2 than from any other class. Likewise, Johnson and colleagues (2005) found that the presence of group B2 *E. coli* was an independent predictor of pyelonephritis as opposed to cystitis in women, indicating the greater ability for organisms from the B2 class to ascend the urinary tract.

Because bacteria can reproduce rapidly, they can quickly adapt to variations in their ecological milieu through genetic mutation and gene transfer (Burmolle, Bahl, Jensen, Sorensen, & Hansen, 2008; Kado, 2009; Ong et al., 2009; Zdziarski et al., 2008). Pathogenic microorganisms have evolved to include a redundancy of virulence factors, which are transferred within and between species. Since uropathogens generally require more than one type of virulence factor to cause clinical disease, the pattern of virulence factor co-expression must be balanced against the likelihood that the virulence factor will trigger a host immune response if the uropathogen is to survive in the host (Hancock &

Klemm, 2007; Zdziarski et al., 2008). Moreover, there is evidence that some virulence factor structures communicate with one another using peptides and other biochemical messengers to maintain a tight balance between pathogenicity and evasion of the host immune system (Hancock & Klemm, 2007; Lane & Mobley, 2007).

The pattern of virulence factor expression and repression depends on the metabolic, ecologic, and evolutionary demands of the microorganism. For example, some strains of uropathogenic *E. coli* express P fimbriae, a type of adhesin, while in the lower urinary tract, but not while in the upper urinary tract (Lane & Mobley, 2007; Snyder et al., 2005). This type of "phase switching" is thought to confer enhanced bacterial survival in the kidney because P fimbriae expression in the kidney would otherwise trigger intense phagocyte chemotaxis to the infected tissue, resulting in elimination of the P-fimbriated uropathogen (Bergsten et al., 2005; Rice et al., 2005; Snyder et al., 2005; Wullt, 2003). However, in order for this microorganism to adhere to the host uroepithelium and avoid hydrodynamic elimination during micturition, they must express another type of adhesin while P fimbriae expression is "switched off" in the kidney (Bergsten et al., 2005). The expression of other adhesins, such as type 1 fimbriae or afimbriated adhesin (Afa), while P fimbriae expression is "switched off" will stimulate a less intense host immune response in the kidney (Snyder et al., 2005).

Most uropathogens express a combination of the following virulence factors: adhesins, invasins, capsules, iron acquisition systems, toxins, and motility. Each of these will be described below.

Adhesins. Adhesins are structures, usually components of fimbriae on the outer surface of microorganisms, which bind with receptors found on the surfaces of host cells

that allow uropathogens to adhere to the epithelial cells lining the urinary tract (Jacobsen, Stickler, Mobley, & Shirtliff, 2008). Adherence is necessary for host invasion and the establishment of infection, and nearly all uropathognic isolates express at least one type of adhesin (Tiba, Yano, & Leite, 2008). Common adhesins include: fimH (found on type 1 fimbriae), PapG adhesin (found on P fimbriae), and Afa/Dr adhesins (Goluszko et al., 2001; Martinez, Mulvey, Schilling, Pinkner, & Hultgren, 2000; Nowicki, Selvarangan, & Nowicki, 2001; Selvarangan et al., 2004; Snyder et al., 2005).

Invasins. Most adhesins also facilitate host cell invasion (Dhakal, Kulesus, & Mulvey, 2008; Duncan, Li, Shin, Carson, & Abraham, 2004). In the bladder, uroepithelial cell invasion results in immune-mediated apoptosis of the infected cell, splotchy sloughing of the uroepithelial lining, and removal of the intracellular uropathogens during voiding of the exfoliated uroepithlium (Martinez et al., 2000; Nicholson, Watts, & Hunstad, 2009). This act of host protection exposes deeper layers of uroepithelium to uropathogens, which may promote hematogenous spread of the microorganism to other body tissues. Furthermore, as uroepithelial cells are replaced over these sloughed areas, uropathogens are buried underneath new cell layers, which may contribute to long-term cystitis and abscess formation in the bladder (Dhakal et al., 2008).

Capsules. Capsules are extracellular polysaccharide structures on pathogenic bacteria that prevent complement opsonization and inhibit phagocytosis (Buckles et al., 2009). Opsonization is an innate host immune defense used to coat “non-self” cells and tissues with complement proteins. Phagocytes recognize these complement proteins and quickly engulf them, along with the pathogen to which they are bound. Through unknown mechanisms, bacterial capsules neutralize complement and delay pathogen

clearance. *E. coli* isolates from *in vitro* and *in vivo* studies of UTI almost universally demonstrate genetic loci for capsule formation (Snyder et al., 2004).

Iron Acquisition Systems. The host and the uropathogen engage in a continuous battle to acquire iron, resulting in the evolution of advanced iron sequestration systems in both organisms (Fischbach, Lin, Liu, & Walsh, 2006; Russo et al., 2002). Iron is an important element for enzymatic function and growth in bacteria, and for oxygen and carbon dioxide transport in humans (Mabbett et al., 2009). Several species acquire iron primarily through the synthesis, release, and recapture of siderophores, which are extremely negatively charged, low molecular weight compounds that have extremely high affinity for ferric iron. Uropathogens use endocytosis to recapture these structures when they are saturated with iron. However, human neutrophils release lipocalin 2, a host protein that binds and deconstructs enterobactin, a specific type of siderophore, preventing the loss of host iron stores to uropathogenic organisms (Goetz et al., 2002). To circumvent this host adaptation, coliform uropathogens have developed salmochelin, a glucosylated form of enterobactin, which evades lipocalin 2 recognition systems and provides uropathogens with a reserve source of iron acquisition (Fischbach et al., 2006).

Toxins. Uropathogens express a variety of toxins, which contribute to the destruction of host tissues, modulation of the host inflammatory response, and alterations in host cell metabolism. Exotoxins are proteins that are produced within the microorganisms and secreted either into or nearby host cells. Common uropathogenic microorganisms produce the following exotoxins: hemolysin-α (HlyA), secreted autotransporter toxin (Sat), and cytotoxic necrotizing factor 1 (CNF-1). Endotoxins are components integrated into the cell walls of Gram-negative pathogens that directly bind

with host immune receptors, such as TLR4, and trigger the synthesis of cytokines. Lipopolysaccharide (LPS) is a common endotoxin found on uropathogens.

Nearly half of all uropathogenic strains of *E. coli* produce HlyA, an exotoxin with concentration-dependent destructive effects on host cells (Y. C. Smith et al., 2008; Soderblom, Oxhamre, Torstensson, & Richter-Dahlfors, 2003). At high concentrations, HlyA directly causes lysis of host cells and tissue sloughing. At low concentrations HlyA interferes with host intracellular calcium-oscillation regulation, which leads to hypersecretion of interleukins 6 (IL-6) and 8 (IL-8) in the kidney, causing profound inflammatory tissue damage. Hemolysin-α is often encoded with fimH (the gene for type 1 fimbriae, a type of adhesin) on a pathogenicity island, and these two virulence factors often occur together in the same organism (Tiba et al., 2008). Secreted autotransporter toxin (Sat) is an exotoxin that is often present in *E. coli* isolates causing pyelonephritis (Maroncle, Sivick, Brady, Stokes, & Mobley, 2006; Restieri, Garriss, Locas, & Dozois, 2007). This protein can induce cytoskeleton changes in host kidney and bladder cells, which weakens the integrity of the cellular structure and causes the cell to rupture (Maroncle et al., 2006). Membrane ruffling is also present, which may lead to epithelial cell macropinocytosis and the uptake of nearby uropathogenic *E. coli* organisms. Cytotoxic necrotizing factor 1 (CNF-1) is an exotoxin that enters the uroepithelial cell and stimulates several destructive events, including: reorganization of the cytoskelton, induction of inflammatory mediators, interference with host cell gene transcription, membrane ruffling, macropinocytosis of nearby uropathogens, retardation and blunting of the host neutrophil response, and prolongation of the host cell life span allowing prolonged host cell inhabitation (Davis, Carvalho, Rasmussen, & O'Brien, 2006; Fabbri

et al., 2002; Fiorentini & Malorni, 2006; Giamboi-Miraglia et al., 2007; Hertting et al., 2008; Miraglia et al., 2007; Real et al., 2007).

Lipopolysaccharide (LPS) is an endotoxin expressed on the cell walls of Gram-negative rods and cocci, including *E. coli* (Brooks, Butel, & Morse, 2004). These complex structures are composed of a series of antigens that directly stimulate a host immune response when they become bound to host TLR4 (Svanborg et al., 2006). Lipopolysaccharide is a key feature of Gram-negative pathogens that cause septic shock, which has an estimated mortality rate of up to 28% (Jaureguy et al., 2007; Russo & Johnson, 2003). LPS triggers the release and activation of IL-1, bradykinin, nitric oxide, tumor necrosis factor (TNF), and macrophages, which causes fever, hypotension, hypercoagulability, and endothelial cell damage seen in septic shock (W. S. Kang, Tamarkin, Wheeler, & Weiss, 2004; Ragnarsdottir et al., 2008; Weng, Wu, Lin, & Liu, 2009).

Motility. Bacterial motility is an important component of virulence and dissemination of pathogenesis to the urinary tract (Lane et al., 2005; Lane & Mobley, 2007). This virulence factor facilitates the migration of planktonic bacteria to the kidneys. Flagellae are long helical organelles that extend from within the bacterial cell envelope, and are composed of thousands of flagellin protein subunits (Brooks et al., 2004). Using chemotaxis, these organelles allow for the coordinated movement of flagellated bacteria toward or away from a particular chemical trigger, such as glucose or proinflammatory cytokines. Furthermore, the "H" antigen is found on this organelle, which triggers a powerful host immune response involving TLR5 (Feuillet et al., 2006). Andersen-Nissen and colleagues (Andersen-Nissen et al., 2007) found that wild-type mice were more

effective in eliminating *E. coli* UTI than mice that were genetically modified to lack TLR5.

Biofilm Formation

A biofilm is a dense bacterial community that adheres tightly to biological and synthetic surfaces. These structures protect uropathogens, such as *E. coli* and *P. mirabilis*, from the host immune response, antimicrobial agents, and the hydrodynamic force of urinary voiding (Ferrieres et al., 2007; D. J. Stickler, 2002; Trautner & Darouiche, 2004; Warren, 2001).

The overall process of biofilm formation is similar between *E. coli* and *P. mirabilis*. First, bacteria adhere to the uroepithelium using type 1 and type 3 fimbriae (Jacobsen et al., 2008; Ong et al., 2009), pili (Merz & Forest, 2002) [RW.ERROR - Unable to find reference:414], and lipopolysaccharide (Razatos, Ong, Sharma, & Georgiou, 1998). Once attached, bacteria secrete extracellular polymeric substance (EPS), which cements the cells together and to the uroepithelium. As EPS accumulates, it traps nearby planktonic bacteria, which in-turn produces more EPS eventually forming a dense multilayered biofilm. *Proteus mirabilis*, like *E. coli*, are coliform bacteria and use fimbriae and other adhesins to colonize the periurethral skin and enter the urinary tract (Rocha, Pelayo, & Elias, 2007). However, *P. mirabilis* has a unique capacity to "swarm" over these surfaces by forming multicellular, elongated, and hyperflagellated rafts, or "swarm cells" that glide over the biofilm using a coordinated pattern of movement (Jones, Young, Mahenthiralingam, & Stickler, 2004). Moreover, Sabbuba and colleagues (Sabbuba, Hughes, & Stickler, 2002) found that these swarm cells were large enough to carry other uropathogenic organisms as they ascend the urinary tract.

Bacteria within a biofilm, or sessile bacteria, undergo genotypic and phenotypic alterations from their planktonic, or free-floating, form to enhance their survival, including: exchange of plasmids that encode for antimicrobial resistance (Blango & Mulvey, 2010), capsule formation (Cuthbertson, Mainprize, Naismith, & Whitfield, 2009; Johnson, 1991; Johnson et al., 2003; Orskov, 1978), altered expression of certain antigens (Domka, Lee, Bansal, & Wood, 2007; Schembri, Kjaergaard, & Klemm, 2003), decreased rate of growth (Donlan & Costerton, 2002; Donlan, 2002), production of enzymes that neutralize antimicrobial agents (He, Li, & Li, 2001), and an increase in overall size (Macleod & Stickler, 2007). Furthermore, bacteria within a biofilm upregulate the expression of quorum-sensing molecules on their cell surface (Domka et al., 2007). Quorum sensing provides these sessile bacteria with information about population density within a biofilm (Parsek & Greenberg, 2005), and bacteria near the edge of the biofilm detach to seek out new colonies when their current environments can no longer support further growth (A. Jain, Gupta, Agrawal, Khare, & Jain, 2007; Lindsay & von Holy, 2006).

Because microorganisms living in a biofilm are less likely to stimulate a host immune response than those in planktonic form, which are capable of swimming freely in the urine and binding with uroepithelial immune sentinel structures, and their expression of virulence factors is downregulated, these uropathogens are thought to serve as reservoirs of infectious organisms rather than as direct contributors to infection (Anderson, Martin, & Hultgren, 2004; Justice, Hunstad, Seed, & Hultgren, 2006).

Host Characteristics of UTI

The host defensive strategies against uropathogens are complex and involve both innate and acquired branches of the human immune system. Components of the innate immune system are responsible for detection and initial clearance of uropathogens, while components of the acquired immune system are responsible for antigen-specific recognition and rapid clearance of subsequent UTI caused by the same uropathogenic species. Moreover, the human urinary tract has a cadre of processes and structures that prevent the pathogenic invasion of the urinary tract tissues, but are not necessarily part of the host immune system, including micturition and soluble host antimicrobial defenses. This section will utilize a three-step framework, modified from a two-step framework proposed by Bergsten and colleagues (Bergsten et al., 2005), to describe the host defenses against uropathogens.

Step One: Preventative Host Processes and Structures

During normal physiological development, the host develops strategies to prevent the bacterial invasion of the urinary tract tissues. These processes and structures are not a true host response to uropathogens, but instead represent an inherent system of host protection that minimizes the likelihood that bacteria will survive in the urinary tract and trigger an immune response.

Micturition, or voiding, clears the contents of the bladder, which includes urine, sediment, and planktonic microorganisms (Moxnes & Hausken, 2006). Normal voiding is the result of synchronized contraction and relaxation of the detrusor and the voluntary and involuntary urinary sphincters; when the detrusor contracts, the sphincters should relax and allow urine to pass (Fowler, Griffiths, & de Groat, 2008). The functional status

of this reflex determines the rate of urinary flow (Yoshimura & Chancellor, 2007). Micturition-related clearance of urinary microorganisms is a function of urinary flow rate and adhesin-mediated bacterial adherence to bladder cells. Decreased urinary flow, as in prostatic hyperplasia, and normal or high bacterial adherence may result in accumulation of bacteria in the urinary tract and activation of the host immune response (Stern, Hsieh, & Schaeffer, 2004; Truzzi, Almeida, Nunes, & Sadi, 2008).

Soluble host antimicrobial defense molecules include alpha- and beta-defensins, Tamm-Horsfall protein, and the complement system. These proteins stimulate several functions of host immune effector cells, as well as interfere with various bacterial functions that are necessary to establish infection.

Defensins. Neutrophil responders to pathogens in the urinary tract produce alpha-defensin, and the renal epithelium produces beta-defensin (Zasloff, 2007). In addition to being directly bactericidal, these molecules can also stimulate mast cell degranulation, neutrophil chemotaxis, and the infiltration of naïve T lymphocytes and dendritic cells (Grigat, Soruri, Forssmann, Riggert, & Zwirner, 2007; Soruri, Grigat, Forssmann, Riggert, & Zwirner, 2007).

Tamm-Horsfall protein. Tamm-Horsfall protein is a substance that is produced in the ascending portion of the loops of Henle (Serafini-Cessi, Malagolini, & Cavallone, 2003). Its primary antimicrobial action is to bind with mannosylated bacterial adhesins, such as fimH, and prevent the adherence of uropathogens to the uroepithelial cell surface (Bates et al., 2004; Raffi, Bates, Laszik, & Kumar, 2005). This protein also activates dendritic cells within the urinary tract, which travel to lymphoid tissue and facilitate the maturation of B and T lymphocytes (Saemann et al., 2005). Antibodies to these proteins

facilitate the removal of pathogens bound to Tamm-Horsfall proteins in the urine (Ratliff, 2005).

Complement. The complement system is characterized by the stepwise activation of several complement enzymes and proenzymes that leads to bacterial opsonization, neutrophil chemotaxis, B lymphocyte activation, and pathogen lysis (Dunkelberger & Song, 2010; Li, Sacks, & Sheerin, 2008). Distinct substances trigger each of the three complement pathways: antigen-antibody complexes trigger the classical pathway, mannose groups on pathogen cell surfaces trigger the mannose-binding lectin pathway, and certain bacterial virulence factors and miscellaneous bacterial structures activate the alternate pathway. Regardless of the source of activation, the complement cascades are highly regulated and result in efficient pathogen destruction and clearance.

Step Two: Immune System Activation

Activation of the host immune system relies upon accurate identification of "non-self" cells and tissues, such as uropathogens. This is achieved using an intricate system of molecular bonds between receptors and receptor-specific ligands, much like a specific key fits into a specific keyhole to unlock a door (Bauer, Muller, & Hamm, 2009). In the context of host-pathogen interactions in the urinary tract, the ligands are pathogen-associated molecular patterns (PAMPs), which are molecules on the cell surface of the planktonic microorganisms. PAMPs are highly conserved within a species and can take the form of peptides, sugars, lipids, or other structures extending from the surface of the pathogen.

As planktonic uropathogens make physical contact with urinary tract epithelial cells, ligands such as LPS and flagellin bind with and activate TLR found on the host

epithelial cell surfaces. Two types of TLR are important in human UTI: TLR4 and TLR5. TLR4 binds with LPS (Chow, Young, Golenbock, Christ, & Gusovsky, 1999; Komai-Koma, Gilchrist, & Xu, 2009; Ragnarsdottir et al., 2008; Saemann et al., 2005), and TLR5 binds with flagellin (Andersen-Nissen et al., 2007; Feuillet et al., 2006). When these ligands bind with their respective TLR, an intracellular signaling cascade is initiated, this results in profound cytokine production and recruitment of immune effector cells to the site of infection (Bauer et al., 2009; Foster & Medzhitov, 2009; Takeuchi et al., 2000).

Cytokines and chemokines are proinflammatory mediators that facilitate various functions of the innate and acquired immune responses to uropathogens. Those involved in this response include: tumor necrosis factor alpha (TNF-a), IL-1a, IL-1b, IL-6, and IL-8 (Ragnarsdottir et al., 2008; Rodhe et al., 2009; Svanborg et al., 2001; Weng et al., 2009). A major function of these proteins is to recruit neutrophils to the site of infection. Early evidence demonstrated that Gram-negative bacteria in mice led to increased IL-6 production in the urinary tract, which was followed by an increase in the concentration of urinary leukocytes (de Man et al., 1989; Hedges, Anderson, Lidin-Janson, de Man, & Svanborg, 1991; Olsson, Wheeler, Sessa, & Weiss, 1998). It was later discovered that TLR4 was responsible for the detection of LPS on Gram-negative uropathogens (Backhed, Soderhall, Ekman, Normark, & Richter-Dahlfors, 2001), and that secretion of IL-6, IL-8, and IL-1b was dependent on activation of TLR4 (Samuelsson, Hang, Wullt, Irjala, & Svanborg, 2004). Further studies revealed that specific virulence factors of uropathogens stimulate cytokine release *in vitro* and *in vivo* (Betis et al., 2003; Chromek et al., 2005; Frendeus et al., 2001; Samuelsson et al., 2004).

Urinary secretory immunoglobulin A (sIgA) is an antibody secreted by epithelial cells in the bladder mucosa that recognizes specific antigen targets on uropathogens and opsonizes these microorganisms to facilitate their phagocytic elimination. Although the urinary concentration of sIgA is highest in patients with acute UTI, this antibody has also been found in the urine of elderly patients with asymptomatic bacteriuria (Ethel, Bhat, & Hegde, 2006; L. E. Nicolle & Brunka, 1990), indicating that this substance may serve a role in UTI prevention (Svanborg-Eden & Svennerholm, 1978). Despite the importance of sIgA in neutralizing uropathogens and recognizing subsequent infection with uropathogens possessing homologous antigenic structures, the rate of UTI in humans with sIgA deficiency is not significantly different from humans without sIgA deficiency (Floege, Boddeker, Stolte, & Koch, 1990). Moreover, some strains of *P. mirabilis* produce ZapA, a protease that inactivates sIgA and other immunoglobulins (Belas, Manos, & Suvanasuthi, 2004). There is evidence that most uropathogenic strains of *E. coli* do not produce immunoglobulin proteases (Russo & Carlino-MacDonald, 2008), although some *E. coli* strains do utilize unknown mechanisms to suppress host inflammatory processes (Lloyd, Smith, Eaton, & Mobley, 2009).

Step Three: Influx of Host Immune Effector Cells

Cytokines and chemokines, which are released in response to activation of TLR on the surface of host uroepithelial cells, are responsible for the recruitment of innate host immune cells to the site of UTI. Neutrophils are a class of granulocytic leukocytes whose primary function is to engulf and destroy bacterial pathogens (Brooks et al., 2004; Condron et al., 2003; W. M. Nauseef & Clark, 2009; W. M. Nauseef, 2008). These cells are the first leukocytes to arrive at a site of infection, often occurring within minutes of

pathogen entry. Once uroepithelial cells release chemotactic proinflammatory mediators, neutrophils leave the capillary and enter the tissue with the highest concentration of cytokines and chemokines (W. M. Nauseef & Clark, 2009). This involves four major steps: rolling adhesion, integrin activation, firm adhesion, and transmigration (Ley, Laudanna, Cybulsky, & Nourshargh, 2007; Muller, 2003; Zarbock & Ley, 2009). Velcro-like proteins on vascular endothelial cells, known as selectins, loosely bind to circulating neutophils as they approach the site of infection. As the neutrophil rolls along the vessel wall, selectins slow its forward motion, and the contact time between the neutrophil and each endothelial cell increases. Beta-2 integrins on these slowly tumbling neutrophils are activated and bind with intercellular adhesion molecules on the surface of endothelial cells. Near the site of infection, integrins trigger a change in the shape of the neutrophil from spherical to roughly flat, and the neutrophil adheres tightly to the vessel wall. Flattened neutrophils squeeze between and perhaps through endothelial cells and follow the concentration gradient of chemotactic stimuli, such as IL-8, to the source of infection. Neutrophil transmigration between the blood vessel and the infected tissue occurs quickly, despite the complex interaction of cytokines, chemokines, and neutrophil cytoskeletal structures (Muller, 2002).

After neutrophils arrive at the site of infection, they identify and ingest opsonized pathogens. Opsonizing molecules, such as IgA, complement, alpha- and beta-defensins, and sIgA, coat these microorganisms and facilitate initial binding with neutrophils (McKenzie & Schreiber, 1998; Sengelov, 1995). Ingestion begins when neutrophils bound to opsonized target cells undergo polymerization of actin within the neutrophil cytoplasm, which results in the cell membrane of the neutrophil wrapping around the

pathogen (Griffin, Griffin, Leider, & Silverstein, 1975). When the cell membrane has completely enveloped the pathogen, a phagosome forms (Swanson, 2008). Cytoplasmic granules containing microbiocidal enzymes, such as NADPH oxidase, enter the newly formed phagosome and form a phagolysozome. NADPH oxidase regulates a complex biochemical reaction that results in the release of reaction oxygen species within the phagosome, known as the oxidative burst (Diebold & Bokoch, 2005; W. M. Nauseef, 2008). These toxic oxygen metabolites result in the production of hydrogen peroxide, which is an extremely effective bactericidal agent at the cellular level (W. M. Nauseef, 2008). Other granular enzymes that function in bacterial killing include: myelo-peroxidase, elastase, and metalloproteinase (W. M. Nauseef & Clark, 2009). The lifespan of neutrophils is quite short, and expired neutrophils are ingested and cleared by tissue macrophages (Akgul, Moulding, & Edwards, 2001; Savill et al., 1989).

Manifestations of UTI

Clinical signs and symptoms of UTI provide observable evidence of the complex interaction between pathogen virulence factors and the host immune response. The Centers for Disease Control and Prevention (CDC) recommend the following clinical signs and symptoms to facilitate the standardization of diagnostic criteria for UTI: dysuria, urinary urgency, urinary frequency, suprapubic discomfort, flank discomfort, and fever (Horan, Andrus, & Dudeck, 2008). In addition, delirium is a recognized manifestation of UTI in older adults (Gau et al., 2009; Levy, Eilertsen, Kramer, & Hutt, 2006). This section will describe the pathophysiologic basis for clinical signs and symptoms of UTI.

Dysuria

Dysuria, or painful urination, is a common symptom associated with lower UTI, although it may also be present in noninfectious inflammatory conditions in the lower urinary tract, such as uroepithelial trauma, prostatis, neoplasm, interstitial cystitis, and urinary tract calculi (Bremnor & Sadovsky, 2002). Uropathogenic invasion of host uroepithelial cells leads to the premature apoptosis of these cells, sloughing of the uroepithelial layer, and exposure of subepithelial bladder tissue to the urine. This tissue contains a dense network of afferent myelinated A-delta and unmyelinated C nerve fibers, which are exposed to urine following the loss of the overlying uroepithelial layer. Pain mediators in the urine trigger an intense sensation of pain *vis a vis* these nerve fibers (Parsons, Greenberger, Gabal, Bidair, & Barme, 1998).

A-delta fibers are mechanoreceptors that sense relaxation of the detrusor during bladder filling and contraction of the detrusor during bladder emptying (Yoshimura & Chancellor, 2007). In the bladder and urethra, C fibers are primarily nociceptors that detect irritants in the urine, such as potassium and tachykinins, and may also have mechanosensitive properties when exposed to these irritants (Habler, Janig, & Koltzenburg, 1988).

As urine leaves the bladder during voiding, the stretching of urethral tissue activates A-delta fibers in the urethral subepithelium, and the contraction of the detrusor activates A-delta fibers in the bladder (Shea, Cai, Crepps, Mason, & Perl, 2000). Furthermore, irritants in the urine stimulate C fibers in the bladder and urethral subepithelium as the bladder decompresses and the urethra dilates during voiding (Habler

et al., 1988). Stimulation of both mechanoreceptors and nociceptors in the bladder and the urethra may lead to the sensation of pain during urination in UTI.

Urgency

Urgency, or the intense desire to void that is difficult to defer, is also a common symptom associated with lower UTI. This uncomfortable sensation, which may be exquisitely powerful, can lead to episodes of urge urinary incontinence. The neural mechanism for urgency is similar to that involved with dysuria (Yoshimura & Chancellor, 2007). When the umbrella layer of uroepithelium is sloughed and subepithelial bladder tissue is exposed to irritants in the urine, mechanoreceptors in this tissue are stimulated in an exaggerated fashion. The central nervous system receives messages from these receptors that the bladder is full and voiding is necessary even though there may be very little urine in the bladder.

Frequency

The International Continence Society defines urinary frequency as two distinct entities: daytime frequency and nocturia. Daytime frequency is a patient perception that they void too often during the daytime, while nocturia is the complaint that the patient has to awaken at least once during the nighttime to void (Abrams et al., 2002; Irwin et al., 2006). Urinary frequency is very closed related to urinary urgency in that the patient may experience several episodes of urgency throughout the day and night, most of which result in the patient voiding the contents of their bladder. The basis for urinary frequency is the behavioral response to an exaggerated nociceptor-mechanoreceptor neural response in an inflamed and denuded bladder wall (Yoshimura & Chancellor, 2007). This

unusually strong urge to void is dependent on the concentration of bladder irritants and the extent of uroepithelial damage, and not necessarily the volume of urine.

Suprapubic Discomfort

Mechanoreceptors in the bladder wall, including those that act as nociceptors in the presence of urinary irritants, sense outward pressure from bladder filling as well as inward pressure from external bladder palpation (Yoshimura & Chancellor, 2007). These exposed nerve endings transmit pain and pressure signals along afferent nerve pathways to the brain, which are recognized as pain and tenderness referred to the suprapubic abdominal region. Suprapubic pain, defined as discomfort over the urinary bladder that occurs at rest, may primarily indicate hypersensitivity to outward pressure on the bladder wall during bladder filing. Suprapubic tenderness, defined as discomfort over the urinary bladder that occurs suddenly during palpation of overlying tissue, may primarily indicate hypersensitivity to inward pressure on the bladder wall. Because a very low volume of urine may not cause bladder stretching and distention, a patient with UTI may not experience suprapubic pain at the time of assessment. However, palpation of near-empty bladders may elicit suprapubic tenderness when mechanoreceptors are stretched from an external force. Because clinicians may not be able to assess for suprapubic discomfort at a time when the patient's bladder has an adequate volume of urine to activate mechanoreceptors in the bladder wall, suprapubic tenderness rather than suprapubic pain may provide a more efficient strategy for clinicians to assess for suprapubic discomfort in hospitalized patient with UTI.

Flank Discomfort

Pyelonephritis is an infection of the renal pelvis and parenchyma, and is considered by some to be an upper UTI (Piccoli et al., 2006). Similarly to cystitis, the inflammatory response to uropathogens in the kidney causes renal tissue edema and uroepithelial tissue sloughing (Lane & Mobley, 2007). As inflammatory edema accumulates, mechanoreceptors in the corticomedullary connective tissue and renal pelvis sense changes in interstitial and intrapelvic pressure (Ammons, 1992). Because the kidney is tightly confined within the retroperitoneal space, inflammation-induced edema quickly exerts enormous pressure on these mechanoreceptors resulting in intense discomfort in the ipsilateral flank (Kopp, Cicha, & Smith, 2002; Kopp et al., 2004). Percussion, deep palpation, or closed-fist striking of the costovertebral angle, which is the angle formed by the lateral and downward curve of the 12^{th} rib and the vertical column of the spine (Madsen, Nielsen, & Tisher, 2007), elicits exquisite tenderness in most patients with acute pyelonephritis (Piccoli et al., 2006).

Fever

Fever is a sign of the systemic spread of cytokines from a localized inflammatory response in which the core body temperature (CBT) is elevated significantly above normal. While fever has been recognized as a component of infectious disease and inflammation since ancient times, the physiologic benefits of fever are uncertain (Leggett, 2008). While fever decreases the growth and reproduction of many microbial species, the impact of fever on the virulence of common uropathogens, such as *E. coli* is unknown. Moreover, fever enhances some host immune functions, while inhibiting others (Hasday, Fairchild, & Shanholtz, 2000). For example, fever is known to support the

trafficking of B and T lymphocytes during infection (Appenheimer, Chen, Girard, Wang, & Evans, 2005). However, the capacity for neutrophils to destroy some bacterial species once phagocytosis has occurred is inhibited in the presence of fever (Sebag, Reed, & Williams, 1977). Moreover, the fever response to infection in some older adults is blunted, absent, or reversed (Juthani-Mehta et al., 2005; D. J. Miller, Yoshikawa, & Norman, 1995; Norman, 2000), leading to the removal of fever as a CDC criterion for the diagnosis of UTI in patients over the age of 65 (Horan et al., 2008).

The pathophysiology of fever is complex and involves several phases. In the first phase, cytokines are produced in the urinary tract in response to the presence of uropathogens. Lipopolysaccharide on Gram-negative bacteria, such as *E. coli*, is a particularly efficient trigger for the production of certain pyrogenic, or fever-inducing, cytokines (Steiner et al., 2006). Second, pyrogenic cytokines enter circulation and trigger the peripheral release of prostaglandin E_2 (PGE_2), which enter the blood supply and stimulate the release of additional PGE_2 on the brain-side of the blood-brain barrier endothelium near the hypothalamus (Ivanov & Romanovsky, 2004). Activated PGE_2 receptors on glial cells in the brain trigger the rapid release of cyclic adenosine 5'-monophosphate (cyclic AMP) in the thermoregulatory center of the hypothalamus, which increases the set-point for CBT (Biddle, 2006). To meet this new CBT set-point, heat must be both conserved and generated in a process the patient experiences as chills or shivering. Heat conservation is accomplished through peripheral vasoconstriction, which shunts blood to the vital organs, and behavioral mechanisms such as adding layers of clothing and drinking hot beverages. Heat is generated through the rapid contraction and relaxation of skeletal muscle tissue throughout the body (Leggett, 2008).

As the CBT reaches the new hypothalamic set-point, shivering and vasoconstriction subside (Biddle, 2006). When the CBT exceeds the hypothalamic set-point, peripheral vasodilation occurs resulting in a sensation of excess body heat. This triggers the behavioral responses of shedding layers of clothing and seeking environmental resources that will bring about cooling such as drinking ice water or applying wet washcloths to the forehead. When the hypothalamic set-point suddenly decreases due to the attenuation of glial cyclic AMP release, peripheral vasoconstriction and diaphoresis occur in order to rapidly cool the body and adjust to the new set-point (Biddle, 2006).

Delirium

Delirium is an acute psychobehavioral response to an underlying, usually physiological, disorder that features impairments in attention, cognition, awareness, and judgment (Meagher, Maclullich, & Laurila, 2008). Although delirium has many recognized causes, ranging from uncompensated hearing impairment to terminal cancer, infection has been consistently identified as a significant predictor of delirium in hospitalized patients (Eden, Foreman, & Sisk, 1998; Gau et al., 2009; George, Bleasdale, & Singleton, 1997; Levy et al., 2006). Delirium is associated with increased hospital costs, lengths of stay, mortality, and post-discharge nursing home placement (Han et al., 2010; Rahkonen et al., 2000).

Although the underlying pathophysiological relationship between infection and delirium is poorly understood, a prominent hypothesis is that activation of the peripheral innate immune system triggers the release of cytokines in the central nervous system (Godbout et al., 2005; Henry, Huang, Wynne, & Godbout, 2009; Sparkman & Johnson,

2008). These cytokines, including interferon-α and IL-6, interfere with the normal function of neurons in specific areas of the brain that regulate various cognitive processes, resulting in either hyperactive or hypoactive behavioral features of delirium (Cunningham et al., 2009; Maclullich, Ferguson, Miller, de Rooij, & Cunningham, 2008).

Operational Definitions of UTI

The complex nature of UTI pathophysiology is reflected in the myriad methods used in its measurement. Characteristics of the uropathogen and the host immune response can be measured using standard microbiological and molecular biological strategies. Nurses and other clinicians routinely assess for the presence or absence of clinical signs and symptoms of UTI, although practices are largely unstandardized (Gau et al., 2009; Woodford & George, 2009). This section will synthesize the literature on various strategies used in research and clinical practice to measure characteristics of uropathogens, the host immune response to uropathogens, and clinical signs and symptoms of UTI in adults and older adults.

Uropathogen Characteristics

Several laboratory strategies are used to identify the presence, quantity, and molecular characteristics of urinary microbes. These include the quantitative urine culture (QUC), the urinary nitrite test, Gram's stain, and various molecular techniques. Quantitative urine culture is a standard microbiologic procedure that identifies the presence and concentration of planktonic bacteria in a urine specimen (Pezzlo, 1988). Using a calibrated loop, a small amount of urine is spread across a sheep's blood agar plate and a MacConkey agar plate, the latter of which is able to support the growth of *E. coli*. The plates are allowed to incubate for 18 to 24 hours at 35° Celsius and then

examined for the presence of bacterial colonies (Hall & Woods, 2007). This incubation period may be repeated to allow for the growth of slow-growing microorganisms. Depending on the volume of urine spread across the plate during inoculation, which is determined by the size of the calibrated loop, the number of colonies present will be adjusted to arrive at an approximation of the concentration of bacteria in the urine.

Antimicrobial susceptibility testing is a useful supplement to the QUC, which can provide information about the expression of antimicrobial resistance genes, an important virulence factor among some uropathognic species (Jorgensen & Ferraro, 2009). While the QUC provides clinicians with information about urinary tract bioburden and the expression of antimicrobial resistance genes, it does not provide adequate information to precisely identify the microbial species or to differentiate between pathogenic and nonpathogenic microorganisms.

The presence of urinary nitrite is used to identify the presence or absence of some urinary microbe species (McPherson, Ben-Ezra, & Zhao, 2006). Nitrogen is a key element in the production of peptides and proteins. Most, but not all, potential uropathogens obtain this element through denitrification, a process by which nitrate reductases found in the organism convert nitrate into nitrite (Gonzalez, Correia, Moura, Brondino, & Moura, 2006; Morozkina & Zvyagilskaya, 2007). Nitrate-reducing species of common uropathogens include *E. coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. The nitrite test will be positive when nitrate-reducing bacteria are present in a concentration greater than or equal to 10^5 cfu/mL (McPherson et al., 2006). Because denitrification is a slow process, urine should remain in the bladder for at least 4 hours

(Pezzlo, 1988), although the diagnostic utility of this recommendation has not been tested.

While the validity of urinary nitrite has been examined in several populations and found to be an appropriate test to "rule out" bacteriuria (Deville et al., 2004; St John, Boyd, Lowes, & Price, 2006), it has several limitations. First, it does not provide clinicians with a precise estimate of the concentration of urinary bacteria, which is important when considering the population-specific risk of UTI complications at various cut-off values. Second, it does not differentiate pathogenic from nonpathogenic microorganisms, which may lead to an erroneous diagnosis of UTI instead of asymptomatic bacteriuria. Finally, the presence of virulence factor expression cannot be determined since denitrification does not rely on the presence or absence of genetic material for virulence factors (Gonzalez et al., 2006).

The Gram's stain is an important laboratory test that is used to detect the presence of microorganisms and to differentiate these microorganisms based on structures found in their cell envelopes (Pollock, 1983). Gram-positive bacteria have thick layers of peptidoglycan between their cytoplasmic membrane and capsule, which prevents the leakage of cytoplasmic contents form these microorganisms. Gram-negative bacteria have thinner layers of peptidoglycan, but they possess an outer membrane that contains lipopolysaccharide, an important virulence factor and antigenic structure of Gram-negative microorganisms (Brooks et al., 2004). The LPS layer is of critical importance because it is the ligand for TLR4, a specific class of TLR found on uroepithelium that detects Gram-negative microorganisms (Chow et al., 1999). Since most cases of UTI are caused by Gram-negative coliform bacterial species (Nys et al., 2006), and the host

immune response to uropathogens is triggered when TLR4 interacts with the LPS on Gram-negative microorganisms (Backhed et al., 2001; Bauer et al., 2009), the presence of a Gram-negative microorganism during a urine Gram's stain may provide useful prognostic information about the potential for urinary microbes to elicit a host immune response and contribute to clinical manifestations of UTI. Furthermore, the LPS layer prevents hydrophobic substances and large structures, such as antimicrobial molecules, from entering the cytoplasm of Gram-negative bacteria (Belas et al., 2004; S. P. Smith, Manges, & Riley, 2008). However, this test does not provide information about urinary bacterial concentration, the expression of specific virulence factors, or the exact species of microorganism present in the urine (Wiwanitkit, Udomsantisuk, & Boonchalermvichian, 2005).

Molecular techniques, such as polymerase chain reaction (PCR) and multi-locus sequence typing (MLST) can be performed to identify genotypic and phenotypic features of specific bacterial strains within the urine. This information may be useful in differentiating virulent from avirulent urinary microorganisms (Bidet et al., 2007; Houdouin et al., 2007), which is critical in the differentiation between bacterial infection and bacterial colonization. Recently, Clermont and colleagues (Clermont et al., 2000) developed a PCR-based technique to classify *E. coli* isolates within phylogenetic groups. In *E. coli*, groups A and B1 are considered non-pathogenic, whereas groups B2 and D are considered pathogenic (Johnson et al., 2005). The Clermont technique utilizes PCR to analyze bacterial colonies for the presence or absence of specific genes or DNA fragments: *chuA*, *yjaA*, and a gene fragment designated TSPE4.C2. These genes and gene products were found to be markers of each phylogenetic group of *E. coli* (Blattner et al.,

1997; Bonacorsi et al., 2000; Piatti, Mannini, Balistreri, & Schito, 2008), and the Clermont technique uses their presence or absence, in a two-step dichotomous decision-tree (Figure 1) to differentiate an isolate into one of the four phylogenetic classes (Clermont et al., 2000; Hancock et al., 2009). This technique has high accuracy, particularly when the isolate is in the B2 phylogenetic group (Gobert et al., 2007; Gordon, Clermont, Tolley, & Denamur, 2008).

Host Immune Response

While several host defense mechanisms against UTI can be measured, only three have been studied in a clinical context: urinary cytokines, sIgA, and neutrophils. Cytokines, which are synthesized and released into the bladder tissue in response to activation of TLR on the uroepithelium, have been shown to diffuse into the urine when the urinary tract is infected (Olsson et al., 1998; Rodhe et al., 2009). Their urinary concentrations can be estimated using ELISA and other biochemical tests. While tests for these biomarkers are not commonly performed in the clinical setting, they have been examined for future clinical and scientific use in distinguishing asymptomatic bacteriuria from true UTI and in distinguishing upper UTI from lower UTI (Gurgoze et al., 2005; Jantausch, O'Donnell, & Wiedermann, 2000; Krzemien et al., 2004; Otto, Burdick, Strieter, & Godaly, 2005; Rodhe et al., 2009; Rodriguez, Robles, Marugan, Suarez, & Santos, 2008; Sheu et al., 2006). However, most of these studies have been conducted in children, and results have been contradictory (Rodhe et al., 2009). Elevated urinary concentrations of the following cytokines are useful in distinguishing asymptomatic bacteriuria from UTI: CXCL1, IL-1a, IL-1b, IL-6, IL-8, IL-17a, and TNF-a (Davidoff, Yamaguchi, Leach, Park, & Lad, 1997; Engel et al., 2006; L. E. Nicolle, Brunka, Orr,

Wilkins, & Harding, 1993; Rodhe et al., 2009; Sivick, Schaller, Smith, & Mobley, 2010). Moreover, Davidoff and colleagues (Davidoff et al., 1997) found that the concentrations of urinary IL-1a, IL-1b, TNF-a, and IL-6 were significantly elevated in patients with either low-count (at least 10^3 cfu/mL) or high-count (at least 10^5 cfu/mL) bacteriuria. These studies suggest that quantification of certain cytokines, particularly IL-6 and IL-8, may be useful in differentiating UTI from asymptomatic bacteriuria in community-dwelling older adults. However, there is no data to support their use in hospitalized older adults who may have comorbid inflammatory conditions that have an unknown effect on the concentration of these cytokines in the urine.

Urinary sIgA may have clinical and scientific utility in differentiating asymptomatic bacteiruria from UTI. However, in a small sample of hospitalized children and young adults, an elevated urinary concentration of this antibody was significantly associated with the presence of UTI in children and young adults (Deo & Vaidya, 2004). Alternatively, a subnormal concentration of urinary sIgA was also associated with a significantly increased risk for UTI in female children and adults (Fliedner, Mehls, Rauterberg, & Ritz, 1986; Riedasch, Heck, Rauterberg, & Ritz, 1983), which indicates a potentially bidirectional relationship between the concentration of this biomarker and the concentration and virulence of urinary bacteria. Furthermore, an increased concentration of vaginal sIgA may predispose postmenopausal women to UTI (Schoor, Anderson, Klumpp, & Schaeffer, 2001). Although the relationship between the urinary concentration of sIgA and inherent risk for UTI requires further study in order to be clinically useful, antigen specificity is a unique potential benefit of sIgA, which may help

clinicians more rapidly identify the species of the causative uropathogen (Deo & Vaidya, 2004).

The presence of neutrophils in the urine can be determined using microscopy and leukocyte esterase testing. The advantage of microscopy is that it can be used to directly visualize neutrophils, which may not be readily identified using biochemical tests. The disadvantages of microscopy are that the results are highly variable, depending upon the expertise of the microscopist and the distribution patterns of cells within the urine sample (McPherson et al., 2006).

Leukocyte esterase is an enzyme found in the granules of neutrophils. The concentration of leukocyte esterase increases as the concentration of leukocytes increases in the infected urinary tract (Grinstead, Scott, Stevens, Ward, & Wilson, 1987). A urinary neutrophil excretion rate greater than 400,000 cells per hour was indicative of UTI in noncatheterized adults (Gadeholt, 1968), and this correlated with a urinary white blood cell concentration of 10 cells per microliter of uncentrifuged urine (Graham & Galloway, 2001; Stamm, 1992). Diagnostic validity of the leukocyte esterase test has been examined in several populations, and was found to be useful in "ruling out" UTI (Deville et al., 2004; Lammers, Gibson, Kovacs, Sears, & Strachan, 2001; Nys et al., 2006; St John et al., 2006).

Clinical Manifestations

The presence of clinical signs and symptoms of UTI separates this potentially life-threatening condition from the more benign asymptomatic bacteriuria. However, standardized operational definitions for these signs and symptoms are absent from the literature. Theory-driven assessment techniques for dysuria, urgency, frequency,

suprapubic discomfort, flank discomfort, fever, and delirium will be described in this section.

Dysuria, Urgency, and Frequency

Many patients with UTI experience dysuria, urgency, and frequency during the course of their illness (Kupelian et al., 2009). Existing reports of the clinical significance of these symptoms are based on proxy measures, caregiver reports, and chart reviews (Gau et al., 2009; Medina-Bombardo et al., 2003; Monane et al., 1995). These methods may not accurately reflect the presence, intensity, or meaning of these symptoms in the person with UTI. Moreover, because each person experiences sensory stimuli as a function of their personal beliefs and cultural norms, what is unpleasant to one person may not be unpleasant to another. Furthermore, cultural or personal beliefs may prohibit the person from reporting the true presence of these symptoms, which might be seen as private or embarrassing (Meerabeau, 1999). Based on the conceptual definitions of these symptoms, the clinician might simply ask the patient directly about whether or not each symptom is present, although their responses may not accurately represent the magnitude of uroepithelial tissue destruction and inflammation in the urinary tract. A standardized strategy to assess these symptoms, which should include descriptors of pain quality and severity, may enhance the synthesis of UTI research across studies that use these variables.

Suprapubic and Flank Discomfort

Suprapubic tenderness and flank tenderness are common signs among patients with UTI. Because standardized operational definitions of suprapubic tenderness and flank tenderness are missing from the literature, they must be derived based on the

current understanding of mechanisms of tissue inflammation, mechanoreceptor activation, and human anatomy of the urinary tract. To assess for suprapubic tenderness, the nurse gently palpates the lower abdomen overlying the bladder. Suprapubic tenderness is present if discomfort occurs while the nurse palpates over the bladder. To assess for flank tenderness, the nurse percusses over both sides of the spine at the angle formed at the intersection of the lowest ribs and the spine. If percussion of either of these regions results in a new report of discomfort, flank tenderness is present.

The assessment of discomfort in critically ill patients is a unique challenge. These patients are often sedated and endotracheally intubated, and therefore have difficulty communicating the presence and intensity of discomfort (Jacobi et al., 2002; Kwekkeboom & Herr, 2001). However, because indwelling urinary catheters are necessary in most critically ill patients to monitor fluid balance (Leone, Garnier, Avidan, & Martin, 2004), the assessment of CAUTI-related discomfort (suprapubic tenderness and flank tenderness) is important in this population. There is a paucity of information on discomfort assessment in the ICU setting. While various assessment tools have been proposed for use in this population, only the Behavioral Pain Scale (BPS) has been tested in a variety of ICU types and has demonstrated acceptable psychometric properties (Cade, 2008). The BPS utilizes 3 behavioral indicators of the presence of pain appropriate to the intubated and sedated critically ill adult: movement of the upper extremities, facial expressions that indicate discomfort, and compliance with mechanical ventilation.

In summary, although the assessment of discomfort in patients with cognitive impairment or impairments in verbal communication is a unique clinical challenge, there

are assessment tools with acceptable reliability and validity for the purposes of clinical practice and research. Although these instruments may not be useful in evaluating the intensity of discomfort, they are adequate in identifying the presence or absence of discomfort, particularly in response to painful stimuli. Specifically, the PAINAD can be used to assess discomfort in patients with cognitive impairment, and the BPS can be used to assess discomfort in patients who are sedated and intubated with an endotracheal tube.

Fever

Fever may be present in either cystitis or pyelonephritis, but is most often associated with pyelonephritis. There is considerable debate regarding both the measurement of CBT and the significance of various cut-points used to define fever. Furthermore, advanced age, immunosuppression, and antipyretic medication use may blunt the cytoine response to uropathogens. The temperature achieved during infection may not reach a pre-determined cut-point for fever, regardless of infection presence or severity.

Measurement of CBT, or thermometry, is accomplished using a thermometer placed in an orifice that is anatomically nearby a central vein or artery. CBT can be measured sublingually, rectally, tympanically, under the axillae, in the bladder, or via central venous catheter. These measures have variable accuracy and precision, and some measurements require mathematical adjustment to arrive at a more accurate approximation of CBT. Recent evidence suggests that oral thermometry provides the most valid assessment of CBT (Giuliano et al., 2000; Hooper & Andrews, 2006), even in the presence of oxygen administration, endotracheal intubation, and tachypnea (Cashion & Cason, 1984; Hasler & Cohen, 1982; Moran & Mendal, 2002; Yonkman, 1982).

Oral thermometry can be performed using either a digital or mercury-glass thermometer. Digital thermometers are generally safer than mercury-glass thermometers, which are relatively fragile and may cause physical or chemical injuries if broken. Furthermore, most oral digital thermometers require approximately 1 minute of tissue contact within the sublingual pocket, whereas mercury-glass thermometers generally require 4 to 5 minutes of tissue contact before reaching thermometric equilibrium (Hooper & Andrews, 2006). Therefore, the digital thermometer is the preferred method of thermometry in acutely ill adults.

To assess oral temperature using a digital thermometer, the nurse inserts the "bulb" end of the thermometer into either of the sublingual pockets of the patient's mouth, which are roughly triangular anatomical regions formed by the frenulum, the deep lingual artery, and the sublingual artery on either side of the frenulum. Heat from the deep lingual artery is transferred to thermometer bulb, where the flow of electricity becomes altered to reflect the magnitude of transferred heat. The change in electrical flow is at the bulb end is transmitted to a digital numerical display, which is calibrated to either a Celsius or Fahrenheit temperature scale (Latman, 2003).

Traditionally, the defining cut-point for fever is a CBT greater than or equal to 38.0° Celsius (Horan et al., 2008). Early work in thermophysiology, which utilized a primitive and unreliable form of axillary thermometry, concluded that the mean temperature of healthy adults is 37.0° Celsius, and that a temperature above 38.0° Celsius should be viewed as an indication of illness (Mackowiak & Worden, 1994). However, more recent evidence using population-based samples suggests that the maximum "normal" CBT, defined as the temperature below that of 99% of a sample of healthy

adults, was considerably lower than that identified in earlier work (Mackowiak, Wasserman, & Levine, 1992). Moreover, this maximum CBT changes according to a diurnal rhythm; at 06:00, this temperature is 37.2° Celsius, and at 16:00, this temperature is 37.7° Celsius. However, these results have not been replicated, and the premise that diurnal variation in CBT follows a traditional sleep-wake cycle (i.e. awake during the day, asleep at night) may not apply to many hospitalized patients who have sleep-wake cycle disturbances, impaired physical mobility, or decreased level of consciousness. Furthermore, immunosuppression and other conditions that blunt the inflammatory response to pathogens may result in failure to achieve a core body temperature greater than 38.0 ° Celsius. Therefore, two definitions of fever will be employed: 1) an oral temperature greater than, or equal to, 38.0° Celsius, or 2) an increase in oral temperature by greater than, or equal to, 1 ° Celsius from baseline (Dinarello, Cannon, & Wolff, 1988).

Delirium

The Confusion Assessment Method [RW.ERROR - Unable to find reference:546] (CAM) is a diagnostic algorithm for delirium (Inouye et al., 1990). This instrument is based on the presence of four key features of delirium: acute onset of mental status changes with fluctuating course, inattention, disorganized thinking, and altered level of consciousness. A person with the first two features and either the third or the fourth feature is considered to have delirium. The CAM has been used in many health care settings, including hospitals and nursing homes, and has been tested using physician, nurse, and multidisciplinary team raters (Rudolph et al., 2010; Soja et al., 2008; Tzeng, 2010; Voyer, Richard, Doucet, & Carmichael, 2009; Zou et al., 1998). A recent

systematic review of validation studies of the CAM demonstrated that this instrument has a combined sensitivity of 94%, a combined specificity of 89%, and moderate to high interrater reliability (kappa 0.7 – 1.0) (Wei, Fearing, Sternberg, & Inouye, 2008). Furthermore, these test characteristics were similar between nurse and physician raters. Although this test is brief and easier to use than alternative delirium assessment instruments, the user must have an understanding of the terminology and clinical use of this tool to optimize its reliability and validity for research.

Summary

In summary, UTI is a common and expensive condition in older adults. Several host and pathogen factors interact to produce tissue damage in host uroepithelium, which may or may not result in clinically evident signs and symptoms of infection. In theory, the expression of virulence factors is what sets uropathogens apart from non-pathogenic urinary bacteria, and therefore UTI from asymptomatic bacteriuria. However, current strategies that are used to diagnose UTI in the clinical setting are not able to provide data on the presence or absence of virulence factors. Strategies that utilize molecular methods, such as the PCR-based Clermont technique, may be useful to differentiate pathogenic versus nonpathogenic strains of E. coli and to provide an alternative operational definition of UTI for research.

Catheter-Associated Urinary Tract Infection

Catheter-associated urinary tract infection (CAUTI) is a type of UTI in which the insertion of an indwelling urinary catheter precedes the onset of infection. An indwelling urinary catheter is a hollow flexible tube that is inserted transurethrally or percutaneously into the bladder to provide continuous, usually gravity-dependent, urine drainage.

Because hospitalized adults with short-term urinary catheters are more likely to have transurethrally-inserted rather than percutaneously-inserted, or suprapubic, catheters, this section will focus on the literature pertaining to CAUTI related to short-term transurethrally-inserted indwelling urinary catheters. Specifically, CAUTI epidemiology, pathophysiology, and diagnostic strategies will be described.

Prevalence and Outcomes

Hospital-acquired UTI, which encompasses CAUTI and other types of UTI that occur during hospitalization, account for 40% of all nosocomial infections in United States hospitals each year (Tambyah et al., 2002). Indwelling urinary catheters account for up to 97% of all hospital-acquired UTI, and unnecessary catheter use is common among hospitalized patients (Apisarnthanarak et al., 2007; Gokula et al., 2004; P. Jain, Parada, David, & Smith, 1995; S. Saint, 2000a). Moreover, the duration of catheterization is the most significant factor in predicting CAUTI in the elderly (Beaujean et al., 1997), with each day of catheterization increasing the incidence of CAUTI by 3% to 10% (S. Saint et al., 2002).

Complications from CAUTI are rare, but they can be devastating. Bacteremia occurs in up to 4% of patients with CAUTI, and most cases of nosocomial Gram-negative bacteremia and sepsis are attributable to CAUTI. Other complications of CAUTI include: urinary tract stone formation, urinary incontinence, bladder outflow obstruction, and antimicrobial resistance.

Pathophysiology

While there are several similarities between the pathogenesis of UTI and CAUTI, there are some important differences. First, the microbiologic characteristics of CAUTI

are different from those of UTI. Briefly, bacteria that cause CAUTI express a somewhat different armamentarium of virulence factors than those that cause UTI (Jacobsen et al., 2008; Juthani-Mehta et al., 2007; Sabbuba et al., 2002), and fungi are more likely to cause CAUTI than UTI due to differences in environmental flora, host immune function, and patterns of antimicrobial use (L. E. Nicolle, 2005; Tambyah & Maki, 2000b). Second, the indwelling urinary catheter compromises many host defenses in the urinary tract, which provides microorganisms with an unrestricted capacity to invade the host and persist in the uroepithelium (Ferrieres et al., 2007; Trautner & Darouiche, 2004). These pathophysiological differences are reflected in the somewhat disparate clinical manifestations of these two conditions (S. Saint, 2000b; Tambyah & Maki, 2000a). This section will describe the microbiologic characteristics of CAUTI, the effects of the urinary catheter on the integrity of host defenses, and the clinical manifestations of CAUTI in greater detail.

Microbiologic and Mechanical Characteristics of CAUTI

Characteristics of both uropathogens and the indwelling urinary catheter contribute to the pathophysiology of CAUTI in important ways. This section will describe how uropathogens interact with the indwelling urinary catheter to establish infection in the host urinary tract.

While *E. coli* is the most common causative organism in both CAUTI and UTI, non-*E. coli* isolates, such as *Pseudomonas aeruginosa,* are more common in CAUTI than in other types of UTI (Ko et al., 2008). In particular, fungal organisms such as *Candida albicans* are the second most common causative organisms in CAUTI in the hospital setting (Hidron et al., 2008; Ko et al., 2008). Other bacterial species that are common

among patients with CAUTI include: *Proteus mirabilis, Enterococcus* species, *Klebsiella pneumoniae, Enterobacter* species, and *Staphylococcus epidermidis*.

Many environmental microorganisms gain entry to the catheterized urinary tract during catheter insertion (Barford, Anson, Hu, & Coates, 2008). Although urinary catheterization is considered a sterile procedure, poor perineal hygiene and inadequate pre-catheterization skin disinfection may contribute to the initial inoculation of microbes into the bladder. While some of these microorganisms remain in the bladder, evidence from studies of bladder volume, voiding pressure, and bacterial growth in the bladder suggest that most may be flushed out in the immediate post-catheterization void (Boen, Markland, & Cass, 1969; Hinman & Cox, 1966; Hrncir, 1996; Wilde & Carrigan, 2003). However, those that remain may contribute to the development of biofilm on the intraluminal surface of the urinary catheter within one to three days post-catheterization (S. Saint & Chenoweth, 2003).

After the initial catheter contaminants are evacuated from the bladder, microorganisms from the hospital environment, including those on bed linens, hands of healthcare workers, and supplies used for bathing, may ascend the extraluminal and intraluminal catheter surfaces and continue to invade the urinary tract. Although some potential uropathogens are effectively removed during routine catheter cleaning (Tsuchida et al., 2008), those with virulence factors that contribute to CAUTI are able to effectively adhere to the catheter surface and ascend to the bladder (Ong et al., 2009; Snyder et al., 2005; D. J. Stickler et al., 2006). The mechanisms behind this variable pattern of adherence are unclear, but evolutionary pressure to select pathogenic strains that express specific types and combinations of adhesin molecules, thus increasing the

likelihood of pathogen invasion and survival, may be an important feature of the microbiological ecology of CAUTI (Ferrieres et al., 2007). The duration of catheterization is the most significant risk factor for CAUTI, which reflects the ongoing migration of environmental uropathogens to the bladder along the catheter surface (Jones, Mahenthiralingam, Sabbuba, & Stickler, 2005; Matsukawa, Kunishima, Takahashi, Takeyama, & Tsukamoto, 2005; Sabbuba et al., 2002; Trautner et al., 2007).

In general, uropathogens that cause CAUTI express the same types of virulence factors as those that cause UTI, including adhesins, toxins, capsules, IgA proteases, and flagellae (Jacobsen et al., 2008; Ko et al., 2008). However, uropathogens that cause CAUTI utilize the urinary catheter to optimize the function of these virulence factors. For example, uropathogens that express adhesin molecules can adhere to uroepithelial cells in the non-catheterized patient. However, this leads to activation of the host inflammatory response, which threatens the viability of the uropathogen. In a catheterized patient, the catheter provides an immunologically neutral niche that allows uropathogens to reproduce without activating a host immune response (Macleod & Stickler, 2007; Ong et al., 2009; D. J. Stickler et al., 2006). Furthermore, this allows uropathogens to attach tightly to binding sites on the catheter surface as well as the urethral mucosa. Because urine flows through the catheter lumen with very gentle pressure (Bergqvist, Bronnestam, Hedelin, & Stahl, 1980; Wilde & Carrigan, 2003), the bonds between adhesin molecules and catheter binding sites remain intact despite the outward flow of urine. These robust molecular bonds allow uropathogens to remain attached to the catheter surface, ascend the urinary tract, and damage host uroepithelial cells (Jacobsen et al., 2008). Moreover, catheter insertion causes microscopic uroepithelial trauma (Barford et al., 2008;

Garibaldi, Burke, Britt, Miller, & Smith, 1980), which facilitates pathogen entry into suburoepithelial tissues and capillaries. Uropathogens that establish colonies in deeper urinary tract tissues can persist for long periods of time leading to chronic UTI, while those that enter the bloodstream *vis a vis* uroepithelial capillaries can multiply in the blood and trigger a systemic inflammatory response (Dhakal et al., 2008; Duncan et al., 2004; Jaureguy et al., 2007; S. Saint et al., 2006).

On both sides of the catheter tubing (i.e. intraluminal and extraluminal), bacteria form biofilm in the presence of urine, which provides them with protection from the host immune system and from exogenous antimicrobials (Anderson et al., 2004; Blango & Mulvey, 2010; Ko et al., 2008; D. J. Stickler, 2002; Trautner & Darouiche, 2004). There is substantial evidence that *E. coli* phylogenetic groups B2 and D are more likely to express genes that encode for antimicrobial resistance within biofilms (Hancock et al., 2009; Piatti et al., 2008). These structures also provide pathogenic bacteria with opportunities to transfer genes for antimicrobial resistance and other virulence factors to avirulent microorganisms (Burmolle et al., 2008; Ong et al., 2009). Moreover, silicone-based catheter surfaces actually promote biofilm formation involving highly virulent strains of uropathogenic *E. coli* (Ferrieres et al., 2007; Ong et al., 2009). Furthermore, bacteria cemented in a biofilm are not aspirated during urine specimen collection (Matsukawa et al., 2005), so urine culture results may not truly reflect the bacterial ecology of the catheterized urinary tract.

Biofilm formation is a complex process (Cox, Hukins, & Sutton, 1989; Donlan & Costerton, 2002; Donlan, 2002; Macleod & Stickler, 2007) that begins with the deposition of a conditioning layer on the catheter surface, which consists of urea,

electrolytes, and proteins. Nearby uropathogens adhere to this filmy later, which is rich in energy substrates. Alternatively, uropathogens may establish residence in microscopic imperfections in the catheter surface and subsequently initiate biofilm formation (Cox et al., 1989; Donlan & Costerton, 2002; Donlan, 2002; D. J. Stickler et al., 2006; D. J. Stickler & Morgan, 2008). As bacteria encounter this solid surface, they excrete exopolysaccharide glue that cements the uropathogens together and to the catheter surface. Nearby planktonic bacteria become trapped in this glue and add to the developing biofilm [RW.ERROR - Unable to find reference:565] (Koseoglu, Aslan, Esen, Sen, & Coban, 2006). This process continues on the catheter surface until the environmental nutrients can no longer support growth of the biofilm community (Parsek & Greenberg, 2005). This complex community behavior is regulated by the upregulation of quorum-sensing molecules, which are used to continuously monitor the concentration of bacteria within the biofilm (Daniels, Vanderleyden, & Michiels, 2004; De Araujo, Balestrino, Roth, Charbonnel, & Forestier, 2010). When a threshold concentration of bacteria in the biofilm is achieved, daughter cells detach from the mature bacteria and enter the urine as planktonic uropathogens (Landini, Antoniani, Burgess, & Nijland, 2010). These newly shed uropathogens can migrate to other areas of the urinary tract, establish a new biofilm, and invade host uroepithelial cells.

Biofilm-forming uropathogens utilize urease to obtain nitrogen from urea, which results in alkalinization of the urine and precipitation of urinary electrolytes. Over time, these precipitates crystallize in the developing biofilm, causing intraluminal encrustation and catheter blockage (D. J. Stickler & Morgan, 2008), which may result in leakage of urine around the catheter and cystoureteral reflux. Urease-producing microorganisms

begin biofilm formation around the catheter drainage eyelets within six hours of catheter insertion, and complete catheter obstruction can occur within 30 hours of catheter insertion (D. Stickler, Young, Jones, Sabbuba, & Morris, 2003).

Host Characteristics of CAUTI

The host immune response to uropathogens is very similar between CAUTI and other types of UTI, although the presence of an indwelling urinary catheter is associated with some important barriers to host protection against uropathogens. This section will describe how the indwelling urinary catheter affects the primary and secondary defenses against infection of the urinary tract and how the materials used to manufacture indwelling urinary catheters may trigger an uroepithelial inflammatory response.

The human host has several primary defenses against uropathogenic invasion of the urinary tract, including urinary sphincters and high-pressure voiding of urine. These protective mechanisms are bypassed in the presence of an indwelling urinary catheter. First, the urinary sphincters serve as one-way valves that permit the voiding of urine from the bladder, but prevent the entrance of environmental microorganisms into the bladder (Trautner & Darouiche, 2004). When the urinary catheter is inserted through the urethra, these sphincters are forced open, and these protective structures cannot close until the catheter is removed. While the purpose of the urinary catheter is to facilitate the drainage of urine from the bladder, it inadvertently functions as a mechanism by which environmental pathogens can bypass the urinary sphincters and gain unabated entrance into the bladder for the duration of catheter use.

Second, the design of indwelling urinary catheters may contribute to the retention of a small volume of urine (Garcia et al., 2007), which serves as a source of nitrogen and

other nutrients to support the growth and reproduction of uropathogens. In catheterized patients, urine is drained from the bladder *vis a vis* two or more drainage eyelets in the proximal tip of the urinary catheter. These eyelets are positioned proximally to the anchoring balloon, which rests in the neck of the bladder. Because the anchoring balloon does not perfectly conform to this anatomical region, urine can pool in the space between the anchoring balloon and the bladder wall, which is distal to the drainage eyelets. This residual urine cannot be evacuated unless the drainage eyelets are repositioned into this space, which does not usually occur until the urinary catheter is removed. In addition to providing nutrients for bacterial growth, urine also provides planktonic bacteria with a medium for motility, which is important for the colonization of new uroepithelial sites (Lane et al., 2005). Since planktonic uropathogens are capable of triggering the host immune response as they attach to uroepithelial TLR, their concentration in retained urine may indicate their potential to cause clinical signs and symptoms of infection in the host.

In addition to circumventing some important primary host defenses, the indwelling urinary catheter affects the surveillance and effector functions of the host immune system. As mentioned previously, Toll-like receptors, such as TLR4 and TLR5, are sentinel immune molecules on uroepithelial cell membranes that detect specific biochemical markers of potential pathogens. Once these receptors bind with their respective ligand, they trigger an intracellular cascade of enzymatic reactions that culminates in the release of cytokines and other inflammatory mediators into nearby tissues and capillaries. These mediators attract neutrophils and other immune effector cells to the site of infection. In the case of UTI, lipopolysaccharide on the outer surfaces

of planktonic Gram-negative microorganisms binds with TLR4 on bladder epithelial cell surfaces. This leads to the production of IL-1, IL-6, IL-8, and other cytokines that attract neutrophils to the bladder. The primary difference in the host immune response between UTI and CAUTI is that heavy biofilm formation on the surfaces of the indwelling urinary catheter allows many CAUTI pathogens to remain in a sessile, or non-planktonic, state (A. Jain et al., 2007). Thus the organisms in biofilm do not make physical contact with the bladder epithelial cells until they detach from the biofilm and "swim" to other sites on the catheter or uroepithelial cell surface.

Some uropathogens in biofilm also interrupt the function of host immune effector cells. Planktonic uropathogens are generally destroyed through a system of antibody- and complement-mediated neutrophil phagocytosis and degradation. However, enzymes produced in the biofilm community protect these microorganisms from antibody and complement, which reduces the phagocytic capability of neutrophils in CAUTI (Cerca, Jefferson, Oliveira, Pier, & Azeredo, 2006; Kristian et al., 2008). Although neutrophils are able to enter biofilm, their ability to detect and ingest nonopsonized uropathogens in biofilm is blunted compared to their ability to detect and ingest planktonic organisms coated with antibody and/or complement. Once ingested, some strains of *E. coli* are able to postpone their own degradation and form viable bacterial microcolonies within neutrophils (Fexby et al., 2007; Nazareth, Genagon, & Russo, 2007). Furthermore, biofilm communities of *P. aeruginosa*, a common uropathogen in CAUTI, utilize quorum-sensing molecules and rhamnolipids to detect and kill approaching neutrophils (Alhede et al., 2009; Van Gennip et al., 2009).

Materials used in the manufacturing of the indwelling urinary catheter may trigger a host inflammatory response that mimics that of a true CAUTI, even in the absence of pathogenic organisms (Crnich & Drinka, 2007). Barford and colleagues (Barford, Hu, Anson, & Coates, 2008) found that physical contact with latex catheter materials triggers the release of IL-6 from human bladder cells *in vitro*, and that cellular damage occurs immediately upon physical contact with these materials. Moreover, the concentration of IL-6 and IL-8 increased over time after bacterial colonies were introduced to the "catheterized" bladder cell cultures. In an *in vivo* canine model, latex catheters produced significant uroepithelial inflammation, while catheters made of silicone, Teflon-coated latex, and polyvinylchloride materials produced only marginal inflammatory changes (Nacey, Delahunt, & Tulloch, 1985). While the mechanism of uroepithelial inflammation resulting from contact with urinary catheter materials is poorly understood, several studies using *in vivo* rat urethra models demonstrate that mechanical irritation of the uroepithelium results in a sensory and autonomic nerve-mediated increase in uroepithelial vascular permeability (Abelli et al., 1991; Liedberg, 1989; Liedberg, Ekman, & Lundeberg, 1990; Nordling, Lundeberg, Ekman, Liedberg, & Theodorsson, 1992).

Clinical Manifestations of CAUTI

The clinical signs and symptoms of CAUTI are similar to those observed in other types of UTI. However, the presence of an indwelling urinary catheter, which is associated with several unique biological phenomena, including biofilm formation, continuous involuntary voiding, and a host inflammatory response to catheter materials, results in some important differences in the clinical presentation of these conditions.

First, because the indwelling urinary catheter continuously drains urine from the bladder, the patient will not intermittently void. Therefore, urinary frequency cannot be measured in patients with an indwelling urinary catheter. Second, dysuria cannot be measured in the catheterized patient since this manifestation requires that the urethral mucosa be intermittently stretched and relaxed to accommodate the passage of urine as it is voided; in the catheterized patient, there is no such intermittent voiding, and the urethral mucosa is continuously stretched to accommodate the indwelling urinary catheter. Therefore, catheterized patients may experience constant urethral pain, but it is not related to the passage of urine, which would otherwise define dysuria. Finally, urinary urgency requires that mechanoreceptors in the bladder wall be activated when the bladder is distended with urine, resulting in the painful urge to empty the bladder. Since the indwelling urinary catheter continuously drains the bladder, this distention is unlikely to occur in the absence of intraluminal catheter obstruction. Therefore, patients with indwelling urinary catheters or CAUTI are unlikely to report dysuria, frequency, or urgency. Notably, these symptoms have been omitted from the most recent Centers for Disease Control and Prevention (CDC) diagnostic criteria for CAUTI (National Healthcare Safety Network, 2010).

The CDC recommends that the following clinical signs and symptoms, in addition to laboratory data (described above), be used to diagnose CAUTI: fever, suprapubic tenderness, and flank tenderness (National Healthcare Safety Network, 2010). In addition, there is strong evidence that delirium may be an important sign of CAUTI in some hospitalized patients (Alagiakrishnan et al., 2009; Inouye & Charpentier, 1996; Van

Rompaey et al., 2009). The Infectious Disease Society of America (IDSA) includes delirium as a clinical manifestation of CAUTI in older adults (Hooton et al., 2010).

Although suprapubic tenderness, flank tenderness, and delirium have been proposed as clinical signs and symptoms of CAUTI, their reliability and validity have not been evaluated in the hospital setting. Furthermore, while fever is an important clinical sign that often triggers clinicians to examine a patient for sources of infection and inflammation (Juthani-Mehta et al., 2005; Levy et al., 2006; Montalvo et al., 2006), it has been shown to have poor specificity for CAUTI (Golob et al., 2008; Orr et al., 1996; Tambyah & Maki, 2000a). However, two studies that examined fever as an indicator of CAUTI relied upon retrospective temperature data found in the medical record (Golob et al., 2008; Tambyah & Maki, 2000a), and the third study occurred in a long-term care facility (Orr et al., 1996). Moreover, Golob and colleagues (Golob et al., 2008) utilized a different definition of fever (38.5 ºC) than that recommended in the CDC diagnostic guidelines (38 °C). Therefore, the validity of these clinical manifestations as indicators of CAUTI in hospitalized adults remains unclear. Moreover, a lack of standardized methods for assessment of these manifestations hampers the examination of their reliability.

Summary

In summary, CAUTI is the most common hospital-acquired infection in the United States. The presence of an indwelling urinary catheter results in a mechanism of infectious disease that is distinct from community-acquired and non-catheter-associated UTI. Biofilm provides an environment for enhanced bacterial adherence, transfer of virulence genes, and protection. In addition, the indwelling urinary catheter itself stimulates a host inflammatory response in the urinary tract. Finally, the indwelling

urinary catheter interferes with the mechanisms necessary for the development of some manifestations that are characteristic of UTI. Therefore, distinct diagnostic guidelines for CAUTI have been established. However, the reliability and validity of the clinical manifestations included in these guidelines has not been examined in hospitalized adults with short-term indwelling urinary catheters.

CHAPTER III

METHODS

Design

This study utilized a cross-sectional design to examine the reliability and validity of the clinical manifestations used to diagnose catheter-associated urinary tract infection (CAUTI) in hospitalized adults with short-term indwelling urinary catheters. A convenience sample of adult inpatients with indwelling urinary catheters was assessed for the presence of 4 clinical manifestations of UTI: fever, suprapubic tenderness, flank tenderness, and delirium.

Each subject was classified as having CAUTI or not having CAUTI using three separate operational definitions of CAUTI. Two definitions were based on the results of quantitative urine cultures, each with different cut values for CAUTI, and the third was based on the results of real-time polymerase chain reaction (PCR) to detect the presence of virulent strains of *Escherichia coli*, the most common pathogen associated with CAUTI. While quantitative urine culture is considered to be the "gold standard" laboratory test to diagnose CAUTI, the results from this test do not necessarily reflect the virulence potential of the prevalent microorganisms. Furthermore, there is debate in the literature regarding the most appropriate cut value to use for a culture-based operational definition of CAUTI. Therefore, the two most commonly used culture-based operational definitions of CAUTI (i.e. [1] at least 10^5 cfu/mL. and [2] at least 10^3cfu/mL) were used to examine the validity of CAUTI manifestations. Because virulence factors determine the disease-causing capacity of microorganisms, the virulence potential of

microorganisms, which can be examined using PCR-based methods, is an essential component of the operational definition of CAUTI.

Research laboratory personnel performed microbiological and molecular analyses, while research nurses performed the clinical assessment of CAUTI manifestations. Both laboratory and clinical research personnel were blinded to the others' results.

Settings and Sample

Three facilities were used as the setting for this study. Site A was a 750-bed university medical center in the Midwest, which served as the setting for the diagnostic validity aims of this study. Sites B and C were each 130-bed community medical centers in the Midwest, which served as the setting for the inter-rater reliability aim of this study. At all three sites, convenience samples were recruited from patients admitted to inpatient medical-surgical, stepdown or intermediate care, and intensive care units (Table A.1). Recruitment occurred over a 5-month period at Site A, and a 1-month period at Sites B and C. Because the study aims differed between these three sites, a slightly different set of inclusion and exclusion criteria were used at each.

Site A

To examine the diagnostic validity of CAUTI clinical manifestations among participants at Site A, these participants were recruited according to the following criteria at baseline: 1)18 years of age or older, 2) had an indwelling urinary catheter placed within 24 hours of the screening study visit, 3) does not have positive urinary nitrite test at screening visit, 4) is not pregnant, 5) does not have cognitive impairment, 6) able to understand and respond to questions in English, and 7) able and willing to provide informed consent. The sample recruited from Site A was restricted to adult patients with

indwelling urinary catheters that were not in place prior to hospitalization. Indwelling urinary catheters placed before hospitalization were excluded for two important reasons: First, this study was intended to address the research problem of CAUTI among patients with indwelling urinary catheters inserted for acute medical reasons, not for chronic use. Second, indwelling urinary catheters quickly become colonized with several microbiologic species, and the number of species increases as the duration of catheterization increases. Therefore, to decrease the probability of polymicrobial bacteriuria, which would have complicated the microbiologic and molecular analyses of the subsequent urine specimens, patients with catheters that had been inserted more than 24 hours prior to the Screening Visit were excluded.

Because quantitative urine cultures do not adequately discriminate hospital-acquired bacterial growth from community-acquired bacterial growth, participants were screened for evidence of any bacterial growth immediately upon study enrollment using a urinary nitrite test. Those with a negative urinary nitrite test result were therefore determined to have neither hospital-acquired nor community-acquired bacterial growth at baseline, making any subsequent bacterial growth reasonably attributable to the indwelling urinary catheter. Participants with a positive urinary nitrite test at baseline, which indicates a significant concentration of community-acquired bacteriuria, were excluded from the study.

Assessment for suprapubic tenderness requires palpation of the lower abdomen. However, in addition to the bladder, this abdominal area also includes organs of the female reproductive system. Although the risk of harm to these organs, or to a developing fetus housed within them, is negligible during lower abdominal palpation, it seemed

prudent for the purpose and scope of this study to forego recruitment of pregnant female participants. Furthermore, discomfort from a childbearing uterus may have introduced a source of bias to assessment of suprapubic tenderness since it could not have easily been distinguished from the pain of an inflamed bladder.

Cognitive impairment can be the result of multiple medical conditions, including acute alcohol intoxication, dementia, and delirium. Because cognitive impairment can develop from myriad additional conditions besides CAUTI, the presence of cognitive impairment at baseline could complicate the assessment of delirium as a specific manifestation of CAUTI. Therefore, patients with cognitive impairment, as evidenced by a score less than 3 on the Six-Item Screener, were excluded from the study sample.

Finally, because the unit of analysis for this study was the catheterized patient, and independence of observations was desired to increase statistical power, only the first episode of catheterization during the study period was included for the study when subjects had more than one episode of catheterization.

A minimum of 75 subjects was required to ensure 90% confidence interval halfwidths of 15% and 10% for estimated sensitivity and specificity, in a population where the prevalence of CAUTI is approximately 30%, 75% of disease patients are expected to test positive, and 75% of non-diseased expected to test negative.

Sites B and C

To examine the inter-rater reliability of three independent nurse assessments of CAUTI clinical manifestations at Sites B and C, participants at these sites were recruited according to the following criteria at baseline: 1) 18 years of age or older, 2) had an

indwelling urinary catheter placed during the current hospitalization, 3) is not pregnant, and 4) is able to understand and respond to questions in English.

Similar to Site A, the sample recruited from Sites B and C was restricted to adult patients with indwelling urinary catheters that were not in place prior to hospitalization. However, in contrast to the laboratory analyses performed on data collected from participants at Site A, only clinical assessment data were collected from participants at Sites B and C. The microbiologic and molecular definitions of CAUTI were irrelevant to the research aim for data collected from Sites B and C, so enrolling participants from these sites based on criteria that would have affected the validity of microbiologic and molecular tests was unnecessary. Therefore, adult patients with an indwelling urinary catheter at the time of the study visit inserted at any time during the current hospitalization were recruited for participation at Sites B and C.

Similar to Site A, pregnant patients were not approached for study enrollment at Sites B and C. Since palpation of the lower abdomen is one of the assessment techniques used to assess for CAUTI clinical manifestations, and unnecessary palpation of this area may result in psychological distress for pregnant patients, particularly in the event of a negative pregnancy outcome (e.g. miscarriage, birth defect), the potential risks involved with assessing these patients were felt to outweigh the potential benefits of their study participation. Therefore, patients who were known to be pregnant were not enrolled at any of the study sites.

Patients at Sites B or C with cognitive impairment at the time of the study visit were approached for study participation, which was not the case at Site A. Since the purpose of data collection at Site A was to identify patients with new onset cognitive

impairment since catheter insertion, which then would have been attributable to catheter-related complications such as CAUTI, it was important to exclude patients at Site A with cognitive impairment at baseline. In contrast, the purpose of data collection at Sites B and C was to compare assessment findings, including that of cognitive impairment, between raters to determine how consistently these findings could be replicated between nurse raters. Since delirium, a form of cognitive impairment, was one of the clinical manifestations of CAUTI being tested in this study, it was essential to be able to enroll patients with this condition at the time of study visit. Therefore, patients at Sites B and C with cognitive impairment at the time of the study visit were not excluded from study participation.

Operational Definition of Primary Study Variables

The primary study variables for this study were CAUTI and the clinical manifestations of CAUTI.

Catheter-Associated Urinary Tract Infection

Catheter-associated UTI was operationally defined in three ways; two based on quantitative urine cultures and the third based on PCR of virulent microorganisms.

Quantitative Urine Cultures

Two culture-based cut values were used to operationally define CAUTI. In the literature, concentrations greater than or equal to 10^5 and 10^3 cfu/mL are proposed as appropriate minimum values for the concentration of any microorganism in the urine in making a clinical diagnosis of CAUTI (Colodner, Eliasberg, Chazan, & Raz, 2006; Hooton et al., 2010; Meyrier & Zalaznik, 2006; Wilson & Gaido, 2004; Woodford & George, 2009). Although one set of guidelines strongly recommends the use of a low

threshold to define CAUTI (Hooton et al., 2010), especially in older adults (Woodford & George, 2009), some clinicians and researchers utilize the higher threshold, which has been one of the standard diagnostic criteria since at least the early 1980's (US Department of Health and Human Services, 1981). In addition, qualitative cultures were performed on each urine sample to identify the species of the most prevalent microorganism in the sample.

The procedure for collecting urine samples was as follows (Mack & Collins, 2004):

- Wash hands and apply non-sterile gloves
- Clamp urinary catheter tubing 6 inches distal to urine sampling port, using a rubberband or C-clamp, for 15-20 minutes. Tubing should remain clamped until the urine specimen is obtained.
- Cleanse urine sampling port with alcohol swab for 3-5 seconds. Ensure that urine sampling port does not come in contact with environmental surfaces (e.g. subject's skin, bed linens). Allow alcohol to dry on sampling port.
- Attach the male end of a 10-mL luer-lock syringe to the urine sampling port.
- Aspirate 10 mL of urine into the syringe.
- Unclamp the rubberband or C-clamp.
- Place a sterile "female end" luer-lock cap onto the "male end" of the luer-lock syringe. Complete the study label and affix it to the side of the syringe:
- Place the samples in a container for transport, surrounded by ice to ensure temporary stagnation of microorganism reproduction, along with completed requisition forms.

- Remove gloves.
- Wash hands.
- Deliver the specimen within 15 minutes to the laboratory of Dr. Daniel Diekema.
- The laboratory procedure for culturing these samples was as follows (Hall & Woods, 2007):
- Mix urine sample gently to avoid foaming and to ensure homogeneous distribution of microorganisms within sample.
- Create serial dilutions:
    - 10^1 Dilution: Transfer 100 microliters of urine sample into 900 microliters of TSB, and mix by pipetting the mixture up and down.
    - 10^2 Dilution: Transfer 100 microliters from the 10^1dilution into another 900 microliters of TSB, and mix by pipetting this mixture up and down.
- Plate the serial dilutions:
    - Place 100 microliters from the urine sample onto a blood agar plate (BAP) and 100 microliters onto an eosin-methylene blue (EMB) agar plate. Spread with a "hockey stick."
    - Place 100 microliters from the 10^1 dilution tube onto a BAP and 100 microliters onto an EMB plate. Spread with a "hockey stick."
    - Place 100 microliters from the 10^2 dilution tube onto a BAP and 100 microliters onto an EMB plate. Spread with a "hocket stick."
- Incubate all plates at 37 ° C in 5% carbon dioxide for 18 to 24 hours.

- Plates were reviewed to determine the appropriate dilution plates by choosing plates that have colonies numbering between 30 and 300. Colonies will be counted and the following equation will be used to determine the counts from the initial sample: cfu/mL = (# of colonies) x (dilution factor [1, 10, or 100]) x 10.
- Organisms present were identified using standard methods of species identification.
- Urine samples were coded according to subject enrollment data and saved for future research.

Presence of Uropathogenic *Escherichia coli*

Second, CAUTI was defined as the presence of *E. coli* at a concentration greater than, or equal to, 10^3 cfu/mL, obtained from the cultures described above, in the phylogenic groups B2 or D. Using *E. coli* isolates from the low threshold culture plates described above, PCR analysis were performed according to the method described by Clermont and colleagues (Clermont et al., 2000):

- Combine the following in a 20+ microliter container suitable for PCR analysis:
    - 2 microliters of 10X buffer (containing *Taq* polymerase)
    - 20 picomoles of the following primers (one primer per mixture):
        - ChuA.1 (5'-GACGAACCAACGGTCAGGAT-3')
        - ChuA.2 (5'-TGCCGCCAGTACCAAAGACA-3')
        - YJaA.1 (5'-TGAAGTGTCAGGAGACGCTG-3')
        - YJaA.2 (5'-ATGGAGAATGCGTTCCTCAAC-3')

        - TspE4C2.1 (5'-GAGTAATGTCGGGGCATTCA-3')
        - TspE4C2.2 (5'-CGCGCCAACAAAGTATTACG-3')
    - 2.2 micromoles each of deoxynucloside triphosphates
    - 2.5 units of *Taq* polymerase
    - 200 ng pure *E. coli* from a culture colony
- Denature each mixture for 5 minutes at 94 ° C
- Perform 30 cycles of the following for each mixture:
    - 30 seconds at 94 ° C
    - 30 seconds at 55 ° C
    - 30 seconds at 72 ° C
- Complete a final extension step of 7 minutes at 72 ° C for each mixture.

A dichotomous decision tree proposed by Clermont and colleagues (Clermont et al., 2000) was used to determine the phylogenetic group for an *E. coli* isolate using the results of the PCR amplification of the *chuA* and *yjaA* genes and the DNA fragment TSPE4.C2 (Figure 1). Briefly, isolates with *chuA* were classified as pathogens since they belong to one of the two pathogenic phylogenetic groups, B2 or D. Isolates without *chuA* were classified as non-pathogens since they belong to one of the two non-pathogenic phylogenetic groups, A or B1. Pathogenic isolates with *yjaA* were classified as belonging to group B2, and those without *yjaA* were classified as belonging to group D. Because pathogenic isolates, by definition, are known to cause disease, subjects from whom group B2 or D *E. coli* is isolated were classified as having CAUTI.

Clinical Manifestations of CAUTI

Although guidelines have been developed that identify clinical manifestations that may indicate CAUTI, descriptions to facilitate the performance of these assessment techniques are absent, unstandardized, or vague such that they lack clinical and research utility. An assessment tool that standardizes their operational definitions and assessment procedures was necessary to facilitate valid and reliable assessment of CAUTI manifestations. Therefore, the CAUTI Assessment of Manifestations Profile (CAMP) was developed by the PI to assess temperature, suprapubic tenderness, flank pain, and delirium (see Appendix C). This tool includes items that require verbal responses of patients.

Because the CAMP, which requires verbal responses, may not be suitable for catheterized patients in intensive care who are continuously sedated and/or mechanically ventilated via an endotracheal tube, the CAUTI Assessment of Manifestations Profile for Sedated and Intubated Patients (CAMP-SI) was also developed by the PI (see Appendix D). The CAMP-SI tool includes the Behavioral Pain Scale (BPS), a behavior-based tool that facilitates the identification of discomfort in patients who are sedated and/or ventilator-dependent. Behavioral indicators of discomfort include: tightened facial expression, finger flexion, and non-compliance with mechanical ventilation.

The CAMP and CAMP-SI were submitted to a panel of 5 experts in UTI diagnosis and management (i.e. 3 physicians and 2 doctorally prepared nurses) for content validation. Three of the five content experts (1 physician and 2 doctorally prepared nurses) responded to the request for instrument review, and all felt that the CAMP and the CAMP-SI were suitable for research purposes, appropriately

parsimonious and would make useful contributions to the literature. However, all respondents were apprehensive that the CAMP-SI may be difficult to use for clinical purposes because it lacked adequate procedural detail to assess suprapubic and flank tenderness. To address these concerns, the CAMP-SI has been modified to provide more cues to guide clinical use, and procedural details on the use of the CAMP-SI was a component of initial rater training on this tool.

This section will describe the procedures used to assess the manifestations used in the CAMP and CAMP-SI.

Fever

Temperature was measured at all visits using a digital oral thermometer (SureTemp Plus Model 692, WelchAllyn). The thermometer was inserted into the subject's left or right sublingual pocket and maintained in this position until an audible signal from the thermometer was produced, indicating that the temperature data was available. The thermometer was calibrated prior to use, according to the manufacturer's instructions. Data regarding the subject's temperature was recorded on the appropriate CRF.

Temperature data were used at Site A to determine diagnostic validity in two ways. First, the temperature at the follow-up visit was used to classify the subject as having, or not having, fever, defined as a temperature greater than, or equal to, 38 °C. Second, the difference in temperature between the follow-up visit and the screening visit was calculated to determine whether or not a clinically significant increase in temperature (i.e. 1 ºC) has developed since the baseline. Temperature changes were calculated to the nearest tenth of a degree, which is the usual level of precision for digital thermometers in

the clinical setting. The diagnostic validity of both of these variables was examined against all three reference standards.

Suprapubic Tenderness

Next, the subjects were assessed for suprapubic tenderness. After exposing the skin between the umbilicus and the mons pubis, the PI or nurse research assistant used the pads of the first, second, and third fingers of the dominant hand to palpate the lower abdomen. Palpation was no deeper than twice the height of the examiner's fingers as they are pressed into the abdominal skin (i.e. no greater than two centimeters). The roughly ovoid shape bounded by the umbilicus superiorly, the superior aspect of the mons pubis inferiorly, and the iliac crests bilaterally were divided into four quadrants, using the abdominal midline and an imaginary line drawn between the two anterior superior iliac spines. The PI or nurse research assistant palpated each quadrant once, as well as the point of intersection formed by the two imaginary lines, using the palpation procedure described above.

During palpation of the suprapubic area, the level of discomfort was examined. All subjects will be asked to indicate the presence or absence of tenderness, using the following scripted prompt:

> "I am going to press gently on your lower abdomen in five different locations. I would like for you to tell me whether or not your level of lower abdominal pain increases while I am applying pressure to each of these five sites. Let me know that your pain is increasing by saying, or nodding your head, 'yes,' or if it is staying the same or getting better by saying, or shaking your head, 'no'."

Research staff assessed participants with oral endotracheal tubes and who were sedated using both the CAMP and the CAMP-SI tools. Research staff assessed participants with oral endotracheal tubes but who were not sedated using only the CAMP

tool. The assessment maneuver and script used for the intubated and sedated sub-sample was the same as that used for non-intubated and non-sedated subjects. However, the rater simultaneously assessed for behavioral indicators of suprapubic tenderness using the Behavioral Pain Scale, which has been embedded into the CAMP-SI.

Flank Tenderness

Next, the subjects were assessed for flank tenderness. After assisting the subject to a sitting or side-lying position (whichever is subject-preferred and not medically contraindicated according to the subject's staff nurse) and exposing the subject's back, the PI or the nurse research assistant gently struck the distal interphalangeal joint of the second finger on the nondominant hand with the tip of the second finger on the dominant hand to percuss the bilateral costovertebral angles. These triangular regions are found at the mid-back and are bound superiolaterally by the 12^{th} ribs, medially by the vertebral column, and inferiorly by the posterior iliac crests. The PI or nurse research assistant percussed both of these regions once, using the percussion procedure described above. During percussion of the costovertebral angles, the level of discomfort was examined. All subjects were asked to indicate the presence or absence of tenderness, using the following scripted prompt:

> "I am going to tap gently on your mid-back in two different locations. I would like for you to tell me whether or not your level of mid-back pain increases while I am tapping each of these sites. Let me know that your pain is increasing by saying, or nodding your head, 'yes,' or if it is staying the same or getting better by saying, or shaking your head, 'no'."

Subjects without sedation or endotracheal tubes were examined using this method alone. However, those who were sedated and had an oral endotracheal tube were examined using two simultaneous measurements for flank tenderness: 1) the method used

in non-intubated and non-sedated subjects, and 2) the Behavioral Pain Scale embedded within the CAMP-SI.

Delirium

Next, subjects were examined for evidence of delirium using the Confusion Assessment Method (Inouye et al., 1990; Wei et al., 2008), which has been embedded into both the CAMP and the CAMP-SI. This manifestation of CAUTI has four indicators: acute onset with fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Data regarding acute onset and fluctuating course were collected from the subject's staff nurse and/or caregiver. Data regarding inattention, disorganized thinking, and altered level of consciousness were collected by direct observation throughout the follow-up visit. Delirium was categorized as "Present" if acute onset with fluctuating course, inattention, and either disorganized thinking or altered level of consciousness are present. If these criteria were not met, delirium was categorized as "Absent".

Operational Definition of Secondary Study Variables

Secondary study variables were measured for participants at Site A in order to examine their influence on the validity of clinical manifestations of CAUTI. These variables included: age, sex, duration of catheterization, concurrent use of a systemic antimicrobial medication, concurrent use of a systemic analgesic medication, concurrent use of an antipyretic medication, and the presence of comorbidities which might manifest as fever, suprapubic tenderness, flank tenderness, or delirium.

Age

Age was defined as the number of years that have elapsed from the recorded patient date of birth found in the subject's medical record. Age data were measured in years as whole numbers between 18 and 120.

Sex

Sex was defined as the presence of either male or female biologic sex characteristics, as documented in the subject's medical record. Sex data were measured categorically, with "M" indicating a male subject and "F" indicating a female subject.

Duration of Catheterization

Duration of catheterization was defined as the number of hours that have elapsed from the time of catheter insertion, as determined during the screening study visit (which occurred within 24 hours of catheter insertion), and the time of urine specimen collection during the follow-up study visit (which occurred 48 to 72 hours after catheter insertion). Since duration of catheterization is known to be the most important risk factor for the development of CAUTI, and the expression of virulence factors may be time-dependent, this variable may moderate the relationship between urinary microbe concentration and the development of clinical manifestations of CAUTI. These data were measured in hours as whole numbers between 60 and 72.

Concurrent Use of a Systemic Antimicrobial Medication

Concurrent use of a systemic antimicrobial medication was defined as the administration of a parenteral or an enteral formulation of an antibiotic or antifungal medication that is known to be effective against CAUTI microorganisms during, or up to 12 hours before, study enrollment. These medications are listed in Table A.2. The

concurrent administration of a systemic antimicrobial medication may affect the species, microbial concentration, or virulence factors present in the urinary tract flora. Data for this variable were obtained from the participant's electronic medication administration record, which provided the time the nurse scans the medication during the medication administration process. Antimicrobial medication use was measured categorically, according to drug class.

Concurrent Use of a Systemic Analgesic Medication

Concurrent use of a systemic analgesic medication was defined as the administration of a parenteral or enteral formulation of an opioid or non-opioid medication during, or up to 4 hours before, study enrollment. These medications are listed in Table A.3. The concurrent administration of analgesic medications may blunt the sensation of discomfort and therefore decrease the sensitivity of measures of tenderness. Data for this variable were obtained from the subject's electronic medication administration record, which provided the time the nurse scans the medication during the medication administration process. Analgesic medication use was measured categorically, according to drug class.

Concurrent Use of an Antipyretic Medication

Concurrent use of an antipyretic medication was defined as the administration of an enteral or rectal formulation of a medication with antipyretic properties during, or up to 4 hours before, study enrollment. These medications are listed in Table A.4. The concurrent administration of antipyretic medications may blunt various biochemical mediators of thermoregulation and therefore decrease the sensitivity of fever. Data for this variable were obtained from the subject's electronic medication administration

record, which provided the time the nurse scans the medication during the medication administration process. Antipyretic medication use was measured categorically, according to the drug name.

Presence of Comorbidities

Comorbidities that might also cause the manifestations of CAUTI (i.e. fever, suprapubic tenderness, flank tenderness, and delirium) were defined as the presence of any of the conditions listed in Table A.5 within the subject's medical record. These comorbidities may decrease the specificity of the manifestations of CAUTI. Each of these conditions was measured dichotomously, as either "present" or "absent".

Data Collection Procedures

Data collection for the research aims that examined diagnostic validity was performed at Site A, as described above, and data collection for the research aims that examined inter-rater reliability was performed at Sites B and C.

Recruitment and Screening

A Screening Protocol (Appendix E) was created to facilitate recruitment at Site A. The electronic medical record software at each site was used to construct an automated case-finding report to facilitate recruitment. The PI constructed this report so that active inpatients who met specific criteria at the time the report was run could be identified. To be included in the report at Site A, the patient must have met the following criteria: (1) age 18 years or older, (2) indwelling urinary catheter inserted within the 24 hours prior to running the report, and (3) have been admitted to a study unit. To be included in the report at Sites B and C, the patient must have met the following criteria: (1) age 18 years

or older, (2) indwelling urinary catheter without restriction as to insertion time, and (3) have been admitted to a study unit.

A Screening Visit case report form was initiated for each potential participant identified through the case-finding report. The electronic medical record for each potential participant was reviewed to determine pregnancy status, demographic data (e.g. age, sex, race, ethnicity), and physical location within the hospital. The PI or research assistant approached all potential participants who met the inclusion criteria, unless his or her nurse or visitor requested the potential participant not be disturbed. If the potential participant was not in his or her hospital room at the time of the visit, the PI or research assistant asked his or her nurse if the potential participant was expected to return, and, if possible, a member of the research team returned at the estimated return time. If the potential participant had still not returned, he or she was removed from the screening list.

If the potential participant was available for the Screening Visit, the staff nurse was asked to approach the potential participant on behalf of the research team to determine if he or she would like to discuss a research study about indwelling urinary catheter use. If the potential participant declined to discuss the study, the PI or research assistant removed him or her from the screening list. If the potential participant agreed to discuss the study, the PI or research assistant initiated discussion of the purpose, data collection procedures, potential risks, potential benefits, and procedure for study withdrawal with the potential participant. The potential participant was provided an opportunity to ask questions about the study. Potential participants who were unable to respond in English, or who could not verbally communicate, were excluded from the study at this time. If agreeable to study participation, the PI or research assistant asked

the potential participant to restate the study's purpose, data collection procedures, potential risks, potential benefits, and procedures for study withdrawal to determine his or her understanding of their participation. If the potential participant was able to do so, he or she was invited to sign the Informed Consent Document and enroll in the study. A signed copy of the Informed Consent Document was given to the participant and a Study ID number was assigned.

A Site A, the Screening Visit Protocol (Attachment 3) was used to screen potential participants for exclusion criteria that would affect the internal validity of study results. The presence of cognitive impairment was examined directly using the Six-Item Screener (SIS), a brief tool that examines one-minute recall of three common items and orientation to day, month, and year. Participants with a score less than three on the SIS, indicating cognitive impairment, were excluded from this study. Bedside urinalysis will be performed to identify the presence or absence of urinary nitrite. To perform this procedure, a member of the study team collected up to one milliliter of urine from the patient's urinary catheter sampling port, using the procedure described above. The rater saturated the nitrite pad of a urinalysis applicator stick, waited a maximum of two minutes to allow for completion of the biochemical test that indicates the presence or absence of nitrite, and then compared the nitrite pad of the urinalysis stick to the reference standard printed on the test kit. Patients with baseline positive urinary nitrite were excluded from this study. If the participant screened positive for baseline UTI using urinary nitrite, or if he or she was determined to have cognitive impairment using the Six-Item Screener, his or her participation in the study was terminated. If the participant screened negative for baseline UTI and cognitive impairment, a Follow-Up Visit was

scheduled for a time period 48 to 72 hours in the future. At Sites B and C, screening for these additional exclusion criteria was not required, so the research team collected study data for all participants who were given a Study ID number at these sites. Screening Visit data were recorded on the Screening Visit CRF (Appendix F).

Since four raters (i.e. the investigator and 3 master's-prepared nurse research assistants) were used to enroll participants and collect study data at Sites B and C, an educational session was developed to ensure accurate understanding and performance of enrollment and data collection procedures. To evaluate ongoing consistency in the performance of these procedures, the investigator met weekly with research assistants to review data collection techniques and to clarify misunderstandings.

Compensation was not provided for study participation. Upon the determination of eligibility, the researcher verbally notified the participant's staff nurse about the participant's study enrollment, and a "Verification of Informed Consent Form" was scanned into the participant's electronic medical record.

Study Procedures

Site A

At Site A, members of the research team collected follow-up data 48 to 72 hours after the subject was enrolled, using the Follow-Up Visit Protocol (Appendix G). This time period allowed for CAUTI to develop under usual circumstances. Subjects who had been discharged from the study institution, transferred to a non-study inpatient unit, had their indwelling urinary catheter discontinued, or who had deceased since the Screening Visit were withdrawn from the study. Study data were recorded on the follow-up visit CRF (Appendix H) and the appropriate version of the CAMP tool. Upon completion of

the Follow-Up Visit, the subject's participation in this study ended. Data regarding the use of sedation and oral endotracheal tubes were collected from the medical record and direct observation, respectively, and recorded on the CAMP-SI tool. Since the use of sedation and mechanical ventilation would universally interfere with verbal communication of discomfort, subjects who were both cognitively impaired and sedated with mechanical ventilation were examined using the CAMP-SI tool.

The PI or research assistant obtained ten milliliters of urine from the urinary catheter sampling port using the procedure described above. This urine sample was delivered to the lab of Dr. Daniel Diekema within 15 minutes for culture and species identification. The concentration and species were recorded on the laboratory data CRF (Appendix I). Laboratory personnel performed PCR processing and analysis to identify phylogenetic group membership for microbiologic isolates with a concentration greater than 1,000 cfu/mL of *E. coli*. The phylogenetic group of *E. coli* isolates was recorded on the laboratory data CRF. The PI reported positive cases of significant bacteriuria to the primary care provider. However, since these results were obtained using a clinical microbiology laboratory (and may not be CLIA-approved), they were not appropriate for use in the clinical setting. Nevertheless, clinicians were able to determine if further clinical urine testing was appropriate based on these research lab findings. Since researchs staff obtained these urine samples during the follow-up visit, and results of quantitative urine culture testing were not available for at least 24 hours after samples were delivered to the laboratory, raters were *de facto* blinded to the results of these tests at the time they assessed for the presence of clinical manifestations.

Sites B and C

Three raters independently collected data during study visits at Sites B and C. Each rater followed the assessment procedures described above to determine the presence or absence of CAUTI clinical manifestations. Each rater assessed the participant independently of the other raters, and the participant was asked not to discuss findings with subsequent raters. Because body temperature and delirium status can change quickly, raters collected these data with minimal delay between raters. After temperature and delirium status data were collected, each rater independently assessed for suprapubic tenderness and flank tenderness. Because palpation of the suprapubic region, percussion of the flank regions, and repositioning to ensure access to these regions would, by definition, elicit discomfort, the participant was provided a 5 to 10 minute rest period between raters when these CAUTI clinical manifestations were assessed. This time period was sufficient to allow the participant to return to his or her baseline level of discomfort after research staff performed potentially uncomfortable procedures (e.g. assisting to the left- or right-lying position, percussing over the flank region, palpating over the suprapubic region).

When all three raters have completed data collection, study participation was terminated for that participant. Members of the research staff reported fever, complaints of discomfort, and delirium to the participant's staff nurse upon completion of the study visit.

Data Entry and Analysis Procedures

Subject data was entered into the RedCap data management software. The PI and nurse research assistant will double enter data to reduce the risk for data entry errors and

will be cleaned using range and consistency checks. This database will be used to compute summary statistics of sample characteristics and to compute inferential statistics for examining differences between CAUTI and non-CAUTI participants.

Measures of central tendency were used to describe the sample characteristics. Nominal-level variables (i.e. sex, race, ethnicity, type of inpatient unit, microbial species, *E. coli* phylogenetic groups, presence of fever, presence of discomfort, and presence of delirium) were described using frequencies and modes. These variables were statistically compared across CAUTI and non-CAUTI groups using either the Fisher's exact test (if group *n* less than or equal to 15 subjects) or the chi-squared test of independence (if group *n* larger than 15 subjects). Ordinal-level variables (i.e. urinary concentration of microbes) were described using medians and were statistically compared across CAUTI and non-CAUTI groups using the Mann-Whitney U test. Normally distributed continuous level variables (i.e. age, temperature, and duration of catheterization) were described using means and standard deviations. These variables were statistically compared across the CAUTI and non-CAUTI groups using an independent samples t-test. Continuous variables that appeared to have non-normal distributions according to descriptive statistics of the sample were described using medians and statistically compared for differences using the Mann-Whitney U test. An alpha level of 0.05 (two-tailed) was employed to identify significant differences between the CAUTI and non-CAUTI groups.

Research Question 1: What is the sensitivity, specificity, PV+, and PV- of each of the clinical manifestations of CAUTI among a sample of hospitalized adults with a short-term indwelling urinary catheter as compared to a cut value of greater than, or equal to, 10^5 cfu/mL of any microorganism (reference standard)?

Four 2x2 contingency tables were constructed. For each, the rows will represent the presence or absence of each manifestation, and the columns will represent the presence or absence of CAUTI using the cut value of 10^5 cfu/mL of any microorganism, as described in Table A.6.

Sensitivity is the quotient of the number of subjects with both CAUTI and fever (A) divided by the sum of all with CAUTI (A+C). This number represents the number of subjects who truly have CAUTI that are correctly identified as such using fever as the indicator of infection.

Specificity is the quotient of the number of subjects with neither CAUTI nor fever (D) divided by the sum of all without CAUTI (B+D). This number represents the number of subjects who truly do not have CAUTI that are correctly identified as such using the absence of fever as the indicator of the absence of infection.

Positive predictive value is the quotient of the number of subjects with both CAUTI and fever (A) divided by the total number of subjects with fever (A+B). This number represents the number of subjects with fever who truly have CAUTI.

Negative predictive value is the quotient of the number of subjects with neither CAUTI nor fever (D) divided by the total number of subjects without fever (C+D). This number represents the number of subjects without fever who truly do not have CAUTI.

Research Question 2: What is the sensitivity, specificity, PV+, and PV- of each of the clinical manifestations of CAUTI among a sample of hospitalized adults with a short-term indwelling urinary catheter as compared to a cut value of greater than, or equal to, 10^3 cfu/mL of any microorganism (reference standard)?

The analysis plan for Research Question 2 was similar to that described for Research Question 1, except that CAUTI was operationally defined as the presence of at least 10^3 cfu/mL of any microorganism. Four 2x2 contingency tables were constructed in an identical manner to those in the analysis plan for Research Question 1.

Research Question 3: What is the sensitivity, specificity, PV+, and PV- of each of the clinical manifestations of CAUTI among a sample of hospitalized adults with a short-term indwelling urinary catheter as compared to a cut value of greater than, or equal to, 10^3 cfu/mL of uropathogenic *E. coli* (reference standard)?

The analysis plan for Research Question 3 was similar to that described for Research Question 1, except that CAUTI was operationally defined as the presence of at least 10^3 cfu/mL of uropathogenic *E. coli* isolates (i.e. those in phylogenetic groups B2 or D). Four 2x2 contingency tables were constructed in an identical manner to those in the analysis plan for Research Question 1.

Research Question 4: What is the inter-rater reliability of each of the CAUTI manifestations in hospitalized adults with a short-term indwelling urinary catheter? Separate analyses will be performed for each CAUTI clinical manifestation. The generalized, or Fleiss', kappa is a statistic that represents the agreement between three or more independent and non-randomly chosen raters on a dichotomous variable. The advantage of this statistic over simpler agreement statistics (e.g. percent concordance) is that it takes into account the possibility that agreement between raters could occur by chance. To examine the statistical significance of these results, which indicates whether or not agreement occurred by chance alone, 95% confidence intervals will be calculated for the kappa statistic of each manifestation. Although guidelines have been published to

guide the interpretation of kappa statistics according to their relative magnitude (e.g. 80% is excellent agreement), these reference ranges do not adequately reflect the measurement context (e.g. measurement bias, overall number of subjects). Therefore, 95% confidence intervals are a more appropriate method to interpret the significance of Fleiss' kappa in this study. Fleiss' kappa and 95% confidence limits will be calculated using the PROC FREQ procedure in SAS.

Research Question 5: What combination of demographic factors, clinical factors, and clinical manifestations of CAUTI provides the composite score with the highest diagnostic validity for CAUTI in a sample of hospitalized adults with a short-term indwelling urinary catheter?

Logistic regression was used to develop a predictive model for CAUTI as a function of clinical manifestations (i.e. fever, suprapubic tenderness, flank tenderness, delirium), demographic factors (i.e. age, sex, race, ethnicity), and clinical factors (i.e. concurrent use of antimicrobial medications, antipyretic medications, analgesic medications, and concurrent comorbidities). These were exploratory analyses only as the sample was not adequately large to perform inferential statistical testing for all secondary study variables.

Protection of Human Subjects

Study procedures were submitted to the Institutional Review Board at the study institutions for approval of the ethical treatment of human subjects. Approval of the appropriate use of nursing services at Site A was also obtained from the Site A Nursing Research Committee. The subjects, or their legal representatives, were presented with verbal and written explanations of the study purpose, procedures, benefits, and risks, as

well as protocols for maintaining confidentiality. Protocols for maintaining confidentiality included: coding of study data to remove individual identifiers (e.g. name, medical record number), reporting study results in an aggregate form with no identification of specific subjects, and restricting access to individual study data by storing it in locked file cabinets and password-protected electronic folders. Participants were informed that participation is voluntary, that the study will require a total of approximately 1-2 hours of their time, and that collection of urine samples from urinary catheters could contribute to infection. Subjects were also instructed on how to contact the investigator with questions or comments, and how to seek medical treatment as an inpatient if an adverse event occurred related to study procedures. Each subject provided informed consent for study participation by signing an informed consent form.

CHAPTER IV

RESULTS OF DATA ANALYSES

Description

Subject data were collected at 3 research sites in the Midwest (1 academic medical center and 2 community hospitals), including a total of 16 inpatient care areas. Urine data were collected from patients at one of these research sites (academic medical center) from nine inpatient care areas. The results of data analyses will be presented in four sections. The first section presents the results of screening and enrollment procedures. The second section describes the participant characteristics and clinical manifestations. The third section describes the validity and inter-rater reliability of clinical signs and symptoms of CAUTI. The fourth section presents exploratory analyses that examine relationships between subject characteristics and the presentation of clinical signs and symptoms of CAUTI.

Screening and Enrollment Results

Site A

Adult patients with recently inserted indwelling urinary catheters were screened for inclusion in the study over an 8-month time period. Table A.7 summarizes the results of screening and enrollment by inpatient unit type. Of the 276 patients who were approached for screening, 269 (97.5%) were eligible to participate in the study. Of the eligible patients, 65 (24.2%) actually enrolled in the study. However, only 27 of these (41.5%; 10% of those eligible) completed all study procedures and were included in the final analysis (Table A.8). The intensive care units had the highest numbers of participants because patients in these areas more often require bladder catheterization

than patients in medical-surgical areas. Of the medical-surgical areas, more patients on the neuroscience (neurology and neurosurgery) unit and the medical cardiology unit were eligible for the study than on general medicine, oncology, and cardiothoracic surgery units because patients with neurological disorders (e.g. spinal cord injury, acute cerebrovascular accident) and medical cardiology disorders (e.g. cardiomyopathy, acute coronary syndrome, heart failure) are more likely to require an indwelling urinary catheter than patients in other types of medical-surgical units. Patients who refused to participate often did so because they felt they were too ill to undergo study procedures (see Table A.8). Of the patients who were excluded based on study criteria, most were excluded because they were intubated and/or sedated, and therefore could not provide informed consent, at the time of the screening visit.

Sites B and C

Adult patients with recently inserted indwelling urinary catheters were screened for inclusion in the study over a 2-month time period. Table A.9 summarizes the results of screening and enrollment by inpatient unit type at Sites B and C. Of the 80 patients who were approached for screening, 30 (37.5%) actually enrolled in the study. The medical-surgical units had the highest proportion of participants because, in comparison to Site A which had several intensive care beds, Sites B and C had many more medical-surgical beds than intensive care beds, and therefore more medical-surgical patients from which to enroll. Patients who declined to participate often did so because they felt they were too ill to undergo study procedures (see Table A.10). Of the patients who were excluded based on study criteria, most were excluded because they were cognitively

impaired and a suitable proxy provider of informed consent for study participation could not be identified at the time of the study visit.

Summary Statistics of Participants and Clinical Manifestations

Site A

Participant Characteristics

Sixty-five participants enrolled in the study, but only 27 completed all study procedures. Table A.11 presents summary statistics of participant characteristics. The mean age of the participants was 63.8 years with most being male, white, and non-Hispanic. The majority of participants were enrolled from the surgical intensive care unit. The mean duration of catheter use prior to enrollment was 14.4 hours.

Using a two-tailed Student's *t* test, the differences in mean age and mean duration of catheter use prior to enrollment between participants and non-participants were non-significant at a 0.05 level of significance ($P = 0.06$ and 0.44, respectively).

Using a Chi-square test of independence, there were no significant differences between participants and non-participants with regard to sex, race, or ethnicity at a 0.05 level of significance ($P = 0.65$, 0.16, and 0.29, respectively).

Clinical Manifestations

Table A.12 presents summary statistics for CAUTI clinical manifestations at Site A. Most of the participants did not have clinical manifestations of CAUTI. Of the four clinical manifestations that were examined, suprapubic tenderness was the most common. Five of the participants had suprapubic tenderness (19%), two had delirium (7.4%), one had fever (3.7%), and one had flank tenderness (5%). The mean temperature at the follow-up visit was 36.78 degrees Celsius, which was 0.065 degrees Celsius warmer than

at the mean temperature at baseline ($p = 0.23$). Seven participants were unable to reposition for flank tenderness assessment (25.9%), mainly due to spinal surgery or lumbago. Five participants had one manifestation (18.5%), and two participants had two manifestations (7.4%). No participant had more than two manifestations.

Twenty-five participants had no growth (92.6%) and two participants had significant bacteriuria (7.4%; Table A.13). Of these, one had growth between 10^3 cfu/mL and 10^5 cfu/mL, and one had growth greater than 10^5 cfu/mL. Two different microorganisms were observed in these participants: one had *E. coli* (3.7%) and one had *Candida glabrata* (3.7%). The *E. coli* colony was phylogenetically classified as belonging to the nonpathogenic B1 group.

Sites B and C

Participant Characteristics

Thirty participants enrolled in the study. Table A.14 presents summary statistics of participant characteristics. The mean age of the participants was 74.3 years with most being white non-Hispanic. An equal number of women and men enrolled in this study. The majority of participants were enrolled from medical-surgical units.

Using a two-tailed Student's *t* test, the difference in mean age between participants and non-participants was non-significant at a 0.05 level of significance ($P = 0.45$). Using a Chi-square test of independence, there was no statistically significant difference between participants and non-participants with regard to sex at a 0.05 level of significance ($P = 0.49$). However, there were fewer Black participants than White participants, and this difference was statistically significant at a 0.05 level of significance

($P < 0.001$). There were no participants or non-participants from other ethnic or racial groups.

Clinical Manifestations

Table A.15 presents summary statistics for CAUTI clinical manifestations at Sites B and C. Most of the participants did not have clinical manifestations of CAUTI. Of the four clinical manifestations that were examined, suprapubic tenderness was the most common, which was consistent with findings from Site A. Ten of the participants had suprapubic tenderness (33.3%), six had delirium (20%), five had fever (16.7%), and five had flank tenderness (16.7%). Sixteen participants were unable to reposition for flank tenderness assessment (53.3%) for at least one rater, mainly due to lumbago or hemodynamic instability. Eleven participants had one manifestation (36.7%), ten participants had two manifestations (33.3%), and one participant had three manifestations (3.3%). No participant had more than three manifestations.

Diagnostic Accuracy of CAUTI Clinical Manifestations

The diagnostic accuracy of CAUTI clinical manifestations was examined from data collected at Site A via research specific aims 1 through 3 and 5. Inter-rater reliability of CAUTI clinical manifestations was examined from data collected at Sites B and C via research specific aim 4. Since the prevalence of bacteriuria at both concentrations was so low, and because none of the participants grew uropathogenic *E. coli*, most of these analyses were performed for academic purposes only.

Research Question 1: The first research question was, "What is the sensitivity, specificity, positive predictive value, and negative predictive value of clinical manifestations to detect significant bacteriuria at a concentration greater than or equal to

10^5 cfu/mL of any microorganism?" A 2X2 table was created for each clinical manifestation. The cells of these tables identified the frequency with which the manifestation yielded a true positive (TP), true negative (TN), false positive (FP), or false negative (FN) result (see Table A.16). Using these values, the sensitivity, specificity, positive predictive value, and negative predictive value of each manifestation was calculated as follows:

- *Sensitivity = TP / (TP - FN)*
- *Specificity = TN / (TN - FP)*
- *Positive Predictive Value = TP / Test Outcome Positive*
- *Negative Predictive Value =TN / Test Outcome Negative*

The sensitivity and specificity of each clinical manifestation, using a bacteriuria concentration greater than, or equal to, 100,000 cfu/mL, are presented in Table A.17. Because there were no positive cases of bacteriuria at this concentration that were positive for CAUTI clinical manifestations, all tested manifestations had a sensitivity and positive predictive values of 0.00. This indicates that none of the cases of significant bacteriuria at this concentration expressed fever, suprapubic tenderness, flank tenderness, or delirium.

In contrast, fever, flank tenderness, and delirium had specificity values of 0.96, 0.95, and 0.92, respectively. Suprapubic tenderness had the lowest specificity value at 0.81. The negative predictive values of these manifestations were also high: 0.96, 0.95, 0.95, and 0.96 for fever, suprapubic tenderness, flank tenderness, and delirium, respectively. This means that most participants without clinical manifestations also do not have significiant bacteriuria at this concentration. The mean specificity of these four

manifestations is 0.91, and the mean negative predictive value is 0.96, indicating that the presence of any of them may be useful in ruling out CAUTI. However, since the prevalence of significant bacteriuria at this concentration was much lower than what has been described in the literature, this finding must be interpreted with caution.

Research Question 2: The sensitivity, specificity, positive predictive value, and negative predictive value of each clinical manifestation, using a bacteriuria concentration greater than, or equal to, 1,000 cfu/mL, follow a similar pattern as for the higher bacteriuria concentration described above (Table A.18). The mean specificity and negative predictive value for this concentration is slightly lower than for the higher bacteriuria concentration, which indicates slightly worse performance of each manifestation at ruling out significant bacteriuria at the 10^3 cfu/mL concentration. Similar to what was observed in Research Question 1, there were no cases of bacteriuria at this concentration that also displayed CAUTI clinical manifestations. Therefore, the sensitivity and positive predictive values are 0.00.

Research Question 3: Question 3 asks, "What are the sensitivity, specificity, positive predictive value, and negative predictive value of clinical manifestations of CAUTI, using a cut value of 10^3 cfu/mL of uropathogenic *E. coli* as the reference standard?" (see Table A.19). Although one participant had this concentration of *E. coli* bacteriuria, it was of a nonpathogenic phylogeny (class B1). Because no participants met this criterion, the sensitivity and positive predictive values of each of these manifestations is 0.00. The specificity and negative predictive values for each of these manifestations is 1.00.

Research Question 4: Question 4 asks, “What is the inter-rater reliability of two nurse’s assessments of CAUTI clinical manifestations?” Data for this research question were collected at Sites B and C. The generalized, or Fleiss’, kappa was calculated for each manifestation using assessment findings from the three study raters. These results are presented in Table A.19. Fever was assessed with the highest inter-rater reliability (K = 1.00) while flank tenderness was assessed with the lowest inter-rater reliability (K = 0.29). Because only 12 participants could be assessed for flank tenderness, the 95% confidence interval for this kappa coefficient was relatively wide and included 0.00, indicating that agreement may have occurred by chance alone. Suprapubic tenderness had slightly higher inter-rater reliability (K = 0.39) than flank tenderness, although its 95% confidence interval did not include 0.00, indicating that agreement among raters was true agreement and not due to chance alone. Therefore, there is insufficient evidence to suggest that nurses can consistently identify flank tenderness in hospitalized patients with indwelling urinary catheters. However, there is evidence to suggest that nurses can consistently identify fever, suprapubic tenderness, and delirium in this population.

Research Question 5: Question 5 asks, “Does age, sex, concurrent use of antimicrobial medications, concurrent use of analgeic medications, or concurrent use of antipyretic medications affect the sensitivity, specificity, positive predictive value, or negative predictive value of CAUTI manifestations?” Given the extremely low prevalence of significant bacteriuria at all definitions, these analyses were not performed as they would not be useful for clinical or scientific purposes. As an academic exercise to illustrate how these analyses would be performed, the diagnostic accuracy of CAUTI

clinical manifestations by age group (younger than 65 years vs 65 years and older) is provided below and summarized in Table A.20.

To examine the influence of age on the expression of CAUTI clinical manifestations, participant age was recoded as “less than 65 years” and “65 years or older”. Among the younger participants (N = 14), 2 participants had significant bacteriuria at the low-threshold conentration (>10^3 cfu/mL), 1 participant had significant bacteriuria at the high-threshold concentration (>10^5 cfu/mL), and no participants had uropathogenic *E. coli*. Among the older participants (N = 13), there were no participants with significant bacteriuria.

The frequency of manifestations by age group is presented in Table A.21. Participants younger than 65 years displayed manifestations of CAUTI more often than older adults (42.9% vs 7.7%, respectively).

The sensitivity, specificity, positive predictive value, and negative predictive value are reported in Tables A.22 through A.24. The mean sensitivity and positive predictive values were 0 for both age groups, indicating that the tested manifestations were not useful for detecting cases of significant bacteriuria at either concentration or uropathogenic *E. coli*. However, the mean specificity and negative predictive values were high in both age groups, but were higher in the elderly group than in the younger group. This may indicate that the tested manifestations may be valid indicators of the absence of significant bacteriuria at both concentrations and uropathogenic *E. coli,* particularly in the elderly.

Summary of Question 5: Because none of the cases developed CAUTI manifestations, the sensitivity and positive predictive values for all manifestations was 0.

However, the specificity and negative predictive values for all manifestations tended to be quite high with either concentration of bacteriuria. However, these results cannot be meaningfully interpreted due to the small sample size used for this study aim, and the results provided for this research question were presented for academic purposes only.

CHAPTER V

CONCLUSIONS

Overview

In this chapter, the discussion of study findings and implications of the findings for practice are presented. Limitations of this pilot study and recommendations for future research are also presented.

Discussion of Study Findings

The discussion of findings is presented in five sections. The first section summarizes screening and recruitment results. The second section summarizes characteristics of participant and urine samples. The third section describes the findings regarding validity of clinical manifestations of CAUTI. The fourth section discusses the inter-rater reliability of clinical manifestations of CAUTI, and the fifth section discusses exploratory analyses.

Screening and Enrollment

Enrollment of participants at Site A was limited by several factors. First, since this site was a tertiary care center and served as a major referral center for unstable and critically ill patients, many of the potential participants were unable to provide informed consent to participate in research. Furthermore, since patients at this site came from a very large geographic area, many did not have a legally authorized representative available to provide informed consent by proxy.

Second, patients at Site A were eligible for study enrollment only if his or her urinary catheter had been inserted within the 12 hours prior to the Screening Visit, at which time the patient was screened for baseline, or community-acquired, urinary tract

infection. This restriction was essential to ensure that participants with pre-existing community-acquired urinary tract infection were not enrolled in the study. However, it precluded the recruitment of patients whose urinary catheters were inserted during a 4-hour block of time during the evening (i.e. 4:00 in the afternoon until 8:00 that night); patients whose catheters were inserted the evening before data collection between 4:00 and 8:00 were not eligible for study enrollment. Therefore, this 12-hour restriction was expanded to a 24-hour restriction to increase the number of potential participants at this site and to prevent systematic bias in participant selection based on the time of catheter insertion.

Third, many participants at Site A either had their urinary catheter removed or were discharged from the facility before the Follow-Up Study Visit. Therefore, the percentage of participants that provided complete study data was much lower than anticipated. The low study completion rate may have been the effect of two institutional initiatives at Site A that the research team did not anticipate at the outset of data collection. One initiative focused on reducing the duration of urinary catheter use on medical-surgical and intensive care units to eliminate CAUTI. The second initiative focused on discharging patients as soon as possible to reduce length of stay. Because this research study was designed to follow the natural course of the participant's hospitalization and catheterization, it would not have been appropriate or ethical to request that the participant's catheter remain in place, or that the participant remain hospitalized, until the Follow-Up Study Visit could be completed.

Finally, conflicting schedules limited the availability of research staff members at Site A to perform concurrent assessment of CAUTI manifestations. Therefore, inter-rater

reliability could not be examined at this site. Two additional sites (Site B and Site C) were added after the initial data collection period, and 3 research staff members were added to the research team at these sites.

Recruitment might have been strengthened using a variety of methods. First, proxy consent providers for patients in the intensive care units may have been more agreeable to permit study enrollment if a member of the patient's clinical care team (e.g. physician, staff nurse) could reassure him or her that the study procedures would not lead to clinical harm. However, this step may have been seen as coercive or threatening since this staff member was also responsible for the patient's clinical care, and the consent proxy provider would reasonably have fear and/or worry of retaliation from this clinical provider for study nonparticipation in the form of compromised or less diligent clinical care.

Second, the use of staff members on each unit who could serve as "recruitment champions" for the study may have boosted participant recruitment through notification of research team members before an indwelling urinary catheter was removed. Since the removal of catheters before the Follow-Up Visit was the main reason for a participant not to complete all study procedures, receiving notification from the clinical staff before the catheter was to be removed may have prevented the loss of this large group of participants. However, the quick removal of urinary catheters at Site A was unanticipated at the start of the data collection period, and receiving approval for clinical staff to have this type of involvement in the study procedures would have required approval from both the Institutional Review Board and the Nursing Research Committee at Site A. Seeking approval from these groups for this protocol change would have significantly delayed

data collection beyond the funding period for this study, thus jeopardizing the recruitment of any participants. Moreover, asking clinical staff to delay catheter removal to await study staff to complete the Follow-Up Visit could be considered unethical as it may increase the risk for infection, injury, debility, and other complications of prolonged catheter use.

Enrollment at Sites B and C was more efficient than at Site A. Several factors may explain this recruitment difference between sites. First, the study procedures at Sites B and C were uncomplicated, mimicked routine clinical care, and were associated with very low risk of causing harm. Moreover, study procedures at Sites B and C were completed in one study visit, whereas the research design for Site A required 2 study visits separated by up to 72 hours.

Patients approached for enrollment at Sites B and C were reluctant to enroll in the study. One reason for this high refusal rate is the sociocultural context of the communities served by Sites B and C. These sites were community-based hospitals, one of which was considered a “safety net” hospital, situated in cities with industry- and manufacturing-driven economies, large indigent and disenfranchised populations, and very limited opportunities for patients to participate in clinical research. Moreover, clinical staff at these sites were largely unfamiliar with the research process and the differing purposes between research and clinical care. Many potential participants, legally authorized representatives, and clinical staff at Sites B and C verbalized suspicion of the research intent, process of obtaining informed consent, or study procedures. Furthermore, some potential participants did not feel comfortable participating in research without approval from their attending physician. These reasons differed from the reasons for

refusal given at Site A, which predominantly focused around the patient's critical illness rather than misperceptions about the research process.

Participant and Urine Samples

Participants

The participants at Site A were predominantly white, non-Hispanic, older females, reflecting the demographics of the surrounding population. A larger proportion of Blacks were recruited from Sites B and C than at Site A, reflecting the more ethnically diverse population served at these sites compared to Site A. However, it is important to note that there were disproportionately fewer Blacks participants than White participants in this sample, and this difference was statistically significant.

The majority of potential participants at Site A were from surgical intensive care units, medical intensive care units, neurology/neurosurgery stepdown units, and cardiothoracic surgery stepdown units. This is consistent with data reports from federal nosocomial infection surveillance programs (Dudeck, Horan, Peterson, et al, 2011), which identified intensive care units (neurology/neurosurgery, medical, trauma, and surgical), neurology/neurosurgery stepdown units, and cardiothoracic surgery stepdown units as having the highest catheter utilization ratios. Conversely, the units with the lowest number of potential participants at Site A were hematology-oncology, general medicine, and surgical oncology, which was also consistent with federal nosocomial infection surveillance data (Dudeck et al, 2011). Differences in catheter utilization ratios between patient care units can be explained, at least partially, through examining the types of patients admitted to each unit. Patients on intensive care, neurology/ neurosurgery stepdown, and cardiothoracic surgery stepdown units are catheterized more

often than those on other units because these patients typically require very precise monitoring of fluid intake and output. Furthermore, patients on intensive care and stepdown units are more likely to be immobile or incontinent due to sedating medications, severe neurological or cardiopulmonary compromise, or physical deconditioning, which precludes the ability to accurately measure urine output without urinary catheterization. In contrast, patients on general medicine or oncology units, though very ill, typically have either better physical mobility (and are therefore more able to void into a measuring device) or have less need for precise fluid intake and output monitoring compared to patients on intensive care or stepdown units.

In contrast, most of the potential participants at Sites B and C were from medical-surgical units, followed by intensive care units, and finally intermediate care units. This enrollment discrepancy (between Site A and Sites B and C) reflects two important differences between the research sites. First, because only a small subset of medical-surgical units granted approval at Site A for the research study (whereas almost all of the intensive care and stepdown units granted approval), the proportion of medical-surgical beds, stepdown unit beds, and intensive care unit beds was weighed more heavily toward stepdown and intensive care beds. This was not a concern at Sites B and C, which granted approval for research on all medical-surgical, stepdown, and intensive care units, so the proportion of medical-surgical beds available for participant recruitment was much higher at these two sites. Second, Site A had an active catheter-utilization reduction initiative as part of its quality improvement program, whereas Sites B and C had a less active catheter-utilization reduction program at the time of data collection, particularly on medical-surgical units. Therefore, medical-surgical patients at Sites B and C were more

likely to have extended catheter duration than those at Site A, which allowed more opportunity to identify these patients as potential study participants. Third, the prospective cohort designed used for data collection at Site A placed temporal restrictions on catheter duration prior to study enrollment, which may have disproportionately affected recruitment of medical-surgical patients who tend to be catheterized for a shorter duration than intensive care unit patients. Since a cross-sectional design was employed at Sites B and C, this type of restriction was not necessary, allowing more medical-surgical patients to be eligible for study participation at these sites.

At all three sites, participants who both enrolled in the study and completed all study procedures were more likely to come from units in which patients tended to have better cognitive function and were physiologically more stable, such as the stepdown, medical, and medical-surgical units. This is likely related to the reluctance of potential proxy providers of informed consent to give permission for the enrollment of critically ill or physiologically unstable family members in a research study. Therefore, a large proportion of eligible patients from intensive care units could not be enrolled, leading to a potential sampling bias toward those participants with better cognitive function (who could therefore provide informed consent for themselves) and better physiologic health on stepdown, medical, or medical-surgical units.

Urine Samples

Urine was collected for urine culture and molecular analysis only at Site A. Most of these urine specimens from participants were sterile (i.e. $<10^3$ cfu/mL; 92.6%), and only two (7.4% of the sample) grew a significant concentration of any microorganism.

One specimen (from an intensive care unit) grew *Candida glabrata*, and one specimen (from a general medicine unit) grew *Escherichia coli*.

Although the number of participants who developed CAUTI was too small for meaningful analysis, these results reflect current trends in CAUTI microbiology. Catheterized patients in an intensive care unit tend to have a higher prevalence of fungal urinary isolates (Talaat, Hafez, Saled, et al, 2010; Temiz, Piskin, Aydemir, et al, 2012), and catheterized patients in a non-intensive care unit tend to have a higher prevalence of bacterial urinary isolates (Tandogdu, Cek, Tenke, et al, 2010). Furthermore, the difference in CAUTI prevalence found in this study between intensive care unit patients and non-intensive care unit patients is consistent with the difference in prevalence between these populations described in the literature, with intensive care unit patients having a higher prevalence of CAUTI than non-intensive care unit patients (Dudeck et al, 2011; Tandogdu et al, 2010).

The *E. coli* isolate identified in this study was nonpathogenic based on its phylogenetic class. This finding is consistent with data that demonstrate a high proportion of asymptomatic *E. coli* bacteriuria relative to symptomatic *E. coli* bacteriuria (i.e. *E. coli* CAUTI) among catheterized patients. However, since only one participant developed *E. coli* bacteriuria in the current study, this finding cannot be meaningfully interpreted.

Diagnostic Validity of CAUTI Clinical Manifestations

Consistency of clinical measurements between multiple raters is imperative to understanding their diagnostic validity. If a clinical measure, particularly one that multiple clinicians will assess at multiple times throughout a hospital stay, cannot provide consistent and interpretable findings, its overall utility for diagnosticians will be

negligible. Therefore, the reliability of the CAMP and the CAMP-SI, which were used to measure manifestations of CAUTI in this study, will be discussed first followed by a discussion of the validity of the clinical manifestations.

Reliability of the CAMP and CAMP-SI

The CAMP tool was tested on all participants at Sites B and C. Because none of the participants were concurrently sedated and intubated, testing of the CAMP-SI could not be performed in this sample. Each item on the CAMP represented one of the clinical manifestations of CAUTI, along with instructions for arriving at a dichotomous interpretation of the assessment finding. According to generalized Kappa statistics, suprapubic tendernes and flank tenderness were identified with fair agreement, delirium was identified with moderate agreement, and fever was identified with perfect agreement. Because these labels are somewhat arbitrary, 95% confidence intervals were calculated for these kappa statistics, which indicated that fever, suprapubic tenderness, and delirium could be identified consistently between nurses in hospitalized patients with indwelling urinary catheters. In contrast, flank tenderness could not be identified consistently between nurse raters, although this may have been due to the small number of participants for whom the research team could safely position to perform the assessment for flank tenderness.

Validity of the CAMP and CAMP-SI

Sensitivity, specificity, positive predictive value, and negative predictive value each address diagnostic validity using different and logically opposite clinical perspectives. Because it is nearly impossible to have a measure that is both perfect at ruling out only true negative and at ruling in only true positives, the goal instead becomes

having the best balance of these tests of validity, in which case all values are as close to perfect as possible. However, in order to accomplish this, there must be variability in both (a) the measure you are testing and (b) the gold standard measure. In this study, there was very little variability in both. Furthermore, there was no concordance between which participants displayed CAUTI clinical manifestations and which participants had positive urine cultures. Therefore, the analyses of diagnostic validity using any of the three "gold standard" measures were without meaning. Although a larger sample size would have been necessary to provide data that would have yielded meaningful results, this pilot study confirmed that the methods used to detect significant bacteriuria and assess for clinical manifestations of CAUTI were feasible.

Implications for Nursing

This study represents an initial attempt to examine the diagnostic validity of four clinical manifestations used to identify CAUTI in hospitalized adults. Although analyses of sensitivity, specificity, positive predictive value, and negative predictive value for these manifestations provided uninterpretable results, some implications for nurses in clinical practice and education can be identified through results of inter-rater reliability analyses and examination of barriers to participant recruitment and retention.

Practicing nurses are in an ideal position to routinely assess and monitor for developing signs and symptoms of infection. This study provides evidence that nurses can agree on the identification of fever, suprapubic tenderness, and delirium in hospitalized patients with an indwelling urinary catheter, although this may not be the case with flank tenderness.

Suprapubic tenderness was found to have only fair inter-rater reliability in this study. This indicates that nurses may be unaware of the most appropriate anatomical locations at which to palpate over the bladder or that the incorrect amount of pressure is being used to perform palpation. In order to effectively induce detrusor muscle stretching, which is felt to be the trigger for suprapubic tenderness in people with urinary tract infection, the area over the bladder must be palpated with adequate pressure and depth to displace the abdominal tissue overlying this organ. However, this depth and amount of pressure is not known, and it is likely highly variable between patients based on the thickness of lower abdominal adipose tissue.

In contrast, delirium was found to have better agreement than suprapubic tenderness among the nurse raters in this study. Identification of delirium, particularly among nurses, is known to be a significant challenge. However, because nurses are available to provide observation over an extended period of time, they are in an ideal position to identify the often subtle changes in cognitive function that often accompany delirium. Because other professionals on the health care team provide only brief observations of the patient's condition, which are separated by long periods of time (often only once per day), detection of delirium requires a monitoring approach that only nurses can provide. Ongoing nationwide efforts to raise awareness of accurate delirium assessment and identification among nurses and other health care professionals may explain the relatively high level of inter-rater agreement found in this study (Gesin, Russell, Lin, et al, 2012; McConnell, Lekan, Bunn, et al, 2009; Mudge, Maussen, Duncan, et al, 2013; Puentes, Bradway, Aselage, et al, 2010; Vasilevskis, Morandi, Boehm, 2011). However, agreement was not perfect between raters despite intensive

training on delirium assessment and identification, which reflects the complex nature of this clinical condition.

Fewer than half of the research participants agreed to being assessed for flank tenderness. This procedure involved assisting the participant to change his or her position, which was unacceptable for patients with severe back pain. Furthermore, participants who have had spinal surgery (e.g. spinal fusion) or recent pelvic/hip surgery (e.g. total hip replacement) were poor candidates for being repositioned to assess for flank tenderness. While this finding may be specific to this sample, it is feasible that the population at-large may similarly refuse to be repositioned for flank tenderness assessment. Moreover, it was unclear if participants declined repositioning because they had been told that participation in research procedures was optional. However, it would have been unethical to require the participants to be repositioned for research purposes. Whether or not these same participants who declined repositioning for research would have similarly declined repositioning as part of their routine clinical care is unclear. Therefore, the feasibility of assessing for flank tenderness in hospitalized adult patients, as well as reasons given for participant refusal to be repositioned, require further investigation.

Limitations

The major limitation of this study is the very small sample size. The study sample consisted of only 2 cases with catheter-associated significant bacteriuria/funguria and only 7 cases with CAUTI clinical manifestations. Moreover, no cases had both bacteriuria/funguria and clinical manifestations. Therefore, findings of this study were reconceptualized as pilot and feasibility for a future, larger study.

Another limitation is the painful and inflammation-based nature of the participant's illness requiring hospitalization. Although exploratory analyses of the effect of comorbid conditions on the diagnostic validity of CAUTI clinical manifestations could not be performed in this study, these conditions may have complicated the assessment of these manifestations, and thus their diagnostic validity and inter-rater reliability. For example, participants with a variety of underlying comorbid conditions, including infection at another site, systemic inflammatory response syndrome (SIRS), or physiologic postoperative inflammation may have produced an elevated body temperature, whether CAUTI was truly present or not. Similarly, participants with lower abdominal or pelvic conditions, such as inflammatory bowel disease, endometriosis, or recent abdominopelvic surgery, may have displayed suprapubic tenderness in the absence of CAUTI. Since Site A served as the tertiary referral center for a large geographical region, excluding patients with these conditions from the study would have further reduced the sampling pool at this research site. Therefore, data were collected on many of these conditions so that their presence could be adjusted statistically, although this step turned out to be unnecessary given the inability to conduct these exploratory analyses given the small sample size.

This points to the potential for suprapubic tenderness to be an assessment finding with little diagnostic utility, particularly in catheterized patients with lower abdominal pain from causes other than CAUTI. In their most recent guidelines for the diagnosis, prevention, and treatment of CAUTI, the Infectious Disease Society of America recommends the following clinical manifestations as suggestive of CAUTI: new or worsening fever, rigors, altered mental status (i.e. delirium), malaise, lethargy, flank pain,

costovertebral angle tenderness (i.e. flank tenderness), acute hematuria, and pelvic discomfort (Hooton, Bradley, Cardenas, et al, 2010). Although the authors gave these signs and symptoms an "A" grade, indicating that good evidence exists to support this recommendation, they report that this evidence came from the opinions of respected authorities based on clinical experience or reports of expert committees rather than high-quality experimental or quasi-experimental studies. Therefore, future research is necessary to empirically examine these manifestations compared to one or more accepted "gold standard" diagnostic criterion for the presence of uropathogens.

An additional limitation of the study is that most of the potential participants who were unable to provide informed consent did not have a proxy provider for informed consent available at the time of data collection. As stated earlier, Site A served as the tertiary referral center for a large geographic region, and these consent proxy providers were often unable to come to the patient's bedside because they had gone to their homes or places of employment. Moreover, obtaining telephone consent from these proxy providers would have been a logistical challenge due to limited research team availability.

The ability to generalize these findings was further limited because participants may not represent all patients with CAUTI. At Site A, nearly 75% of potential participants were excluded due to study criteria, and nearly 60% of those enrolled did not complete the study. At Sites B and C, only 37.5% of potential participants agreed to enroll in the study. This likely produced an enrollment bias in the study sample. While it is clear that the validity findings from this study lack meaning due to the low number of

CAUTI cases, the reliability findings from this study may also lack generalizability to the population of catheterized adults with more than minimal cognitive impairment.

Another limitation was that ongoing efforts at Site A to reduce catheter use and duration introduced a combined historical-sampling bias that may not have been present at other institutions. Had these efforts not been implemented at the time of data collection, it is reasonable to assume that, based on catheter utilization ratios in published hospital-acquired infection surveillance reports (Dudeck et al, 2011), a larger sampling pool would have been available for study recruitment. Instead, only those patients at Site A that were most critically ill or that required aggressive monitoring of fluid balance were permitted to have an indwelling urinary catheter. This historical effect may have then biased the sampling pool toward including only those patients who were too ill to provide informed consent and, therefore, were ineligible for study participation.

Finally, the use of advanced practice nurses as raters limits the generalizability of findings to this population of clinicians. Although advanced practice nurses are in an important position to detect and diagnose CAUTI, they lack the frequent and prolonged patient exposure required for the accurate detection of the highly variable features of delirium. This problem was addressed in this study by having the raters locate the patient's staff nurse, or family member if possible, and ask him or her for information about the patient's baseline attention level, thought organization, and level of consciousness. This baseline information was used to determine the time of onset and fluctuation of course if other delirium features were present. However, information from nursing staff may have been biased if they were unclear how these delirium features were

defined or if they did not have a clear understanding of the patient's baseline cognitive status.

Recommendations for Further Study

This was the first study to examine the validity of clinical manifestations used to identify CAUTI among hospitalized adults with short-term indwelling urinary catheters. This pilot study provided evidence that standardized procedures for assessing clinical manifestations of CAUTI were necessary to facilitate high inter-rater reliability of these assessments. Although the sample size was too small to provide meaningful results about the diagnostic validity of these manifestations, results about the inter-rater reliability of these manifestations appears to provide meaningful information for nurses in clinical or educational roles. Clearly, this study needs to be replicated with a larger and more cognitively diverse sample of hospitalized adults with urinary catheters in order to obtain more meaningful estimates of diagnostic validity of these manifestations. Furthermore, a larger sample would also allow the influence of variables such as age, sex, ethnicity, use of medications (analgesic, antipyretic, and antimicrobial), and presence of comorbid conditions to be examined in a more meaningful way.

Enrolling a more representative sample of patients with urinary catheters from sites with variable catheter management policies would increase the ability to generalize findings to a broader sample of hospitalized patients. Although a total of three sites were used in this study, only one (Site A) was used in a prospective manner that could have been influenced by institutional policies that affected catheter duration (Sites B and C were used in a cross-sectional manner at any time during catheter use, so data were less likely affected by policies that limited catheter duration). Future study designs should

incorporate a variety of hospital types for examination of both diagnostic validity and inter-rater reliability, including academic medical centers, community hospitals, critical access hospitals, and "safety net" hospitals.

Future studies should utilize a sample of raters that represent staff nurses with shift-based assignment of a catheterized patient's care. Having extended opportunities for direct observation and assessment of cognitive status is essential to the accurate interpretation of delirium features, and these opportunities are typically available only to staff nurses that are assigned to provide patient care for an entire work shift. Alternatively, arranging for raters to continually observe patients for an extended period of time to assess for mental status fluctuations may be a suitable approach to garner this information.

Finally, studies that examine the concordance between CAUTI manifestations, clinical and economic complications, cost, and measures of infection based on microbiological and molecular analyses of urine samples need to be conducted. Although this study attempted to examine the presence of four theory-based manifestations of CAUTI against three different "gold standard" laboratory-based criteria for CAUTI, it did not attempt to collect data about CAUTI complications or cost. These analyses can be used to more clearly understand the overall clinical and economic burden of CAUTI manifestations, as well as to clarify diagnostic and treatment guidelines for CAUTI based on the presence of key clinical manifestations.

REFERENCES

Abelli, L., Conte, B., Somma, V., Parlani, M., Geppetti, P., & Maggi, C. A. (1991). Mechanical irritation induces neurogenic inflammation in the rat urethra. *The Journal of Urology, 146*(6), 1624-1626.

Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U., Wein, A. (2002). The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *American Journal of Obstetrics and Gynecology, 187*(1), 116-126.

Abrutyn, E., Mossey, J., Berlin, J. A., Boscia, J., Levison, M., Pitsakis, P., & Kaye, D. (1994). Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? *Annals of Internal Medicine, 120*(10), 827-833.

Akgul, C., Moulding, D. A., & Edwards, S. W. (2001). Molecular control of neutrophil apoptosis. *FEBS Letters, 487*(3), 318-322.

Alagiakrishnan, K., Marrie, T., Rolfson, D., Coke, W., Camicioli, R., Duggan, D.,Wiens, C. (2009). Gaps in patient care practices to prevent hospital-acquired delirium. *Canadian Family Physician Medecin De Famille Canadien, 55*(10), e41-6.

Alhede, M., Bjarnsholt, T., Jensen, P. O., Phipps, R. K., Moser, C., Christophersen, L., Givskov, M. (2009). Pseudomonas aeruginosa recognizes and responds aggressively to the presence of polymorphonuclear leukocytes. *Microbiology (Reading, England), 155*(Pt 11), 3500-3508. doi:10.1099/mic.0.031443-0

Ali, A. S. M., Townes, C. L., Hall, J., & Pickard, R. S. (2009). Maintaining a Sterile Urinary Tract: The Role of Antimicrobial Peptides. *The Journal of Urology, 182*(1), 21-28. doi:DOI: 10.1016/j.juro.2009.02.124

Ammons, W. S. (1992). Bowditch Lecture. Renal afferent inputs to ascending spinal pathways. *The American Journal of Physiology, 262*(2 Pt 2), R165-76.

Andersen-Nissen, E., Hawn, T. R., Smith, K. D., Nachman, A., Lampano, A. E., Uematsu, S., Aderem, A. (2007). Cutting edge: Tlr5-/- mice are more susceptible to Escherichia coli urinary tract infection. *Journal of Immunology (Baltimore, Md.: 1950), 178*(8), 4717-4720.

Anderson, G. G., Martin, S. M., & Hultgren, S. J. (2004). Host subversion by formation of intracellular bacterial communities in the urinary tract. *Microbes and Infection / Institut Pasteur, 6*(12), 1094-1101. doi:10.1016/j.micinf.2004.05.023

Apisarnthanarak, A., Rutjanawech, S., Wichansawakun, S., Ratanabunjerdkul, H., Patthranitima, P., Thongphubeth, K., Fraser, V. J. (2007). Initial inappropriate urinary catheters use in a tertiary-care center: incidence, risk factors, and outcomes. *American Journal of Infection Control, 35*(9), 594-599. doi:10.1016/j.ajic.2006.11.007

Appenheimer, M. M., Chen, Q., Girard, R. A., Wang, W. C., & Evans, S. S. (2005). Impact of fever-range thermal stress on lymphocyte-endothelial adhesion and lymphocyte trafficking. *Immunological Investigations, 34*(3), 295-323.

Backhed, F., Soderhall, M., Ekman, P., Normark, S., & Richter-Dahlfors, A. (2001). Induction of innate immune responses by Escherichia coli and purified lipopolysaccharide correlate with organ- and cell-specific expression of Toll-like receptors within the human urinary tract. *Cellular Microbiology, 3*(3), 153-158.

Barford, J. M., Anson, K., Hu, Y., & Coates, A. R. (2008). A model of catheter-associated urinary tract infection initiated by bacterial contamination of the catheter tip. *BJU International, 102*(1), 67-74. doi:10.1111/j.1464-410X.2008.07465.x

Barford, J. M., Hu, Y., Anson, K., & Coates, A. R. (2008). A biphasic response from bladder epithelial cells induced by catheter material and bacteria: an in vitro study of the pathophysiology of catheter related urinary tract infection. *The Journal of Urology, 180*(4), 1522-1526. doi:10.1016/j.juro.2008.06.012

Bates, J. M., Raffi, H. M., Prasadan, K., Mascarenhas, R., Laszik, Z., Maeda, N.,Kumar, S. (2004). Tamm-Horsfall protein knockout mice are more prone to urinary tract infection: rapid communication. *Kidney International, 65*(3), 791-797. doi:10.1111/j.1523-1755.2004.00452.x

Bauer, S., Muller, T., & Hamm, S. (2009). Pattern recognition by Toll-like receptors. *Advances in Experimental Medicine and Biology, 653*, 15-34.

Beaujean, D. J., Blok, H. E., Vandenbroucke-Grauls, C. M., Weersink, A. J., Raymakers, J. A., & Verhoef, J. (1997). Surveillance of nosocomial infections in geriatric patients. *The Journal of Hospital Infection, 36*(4), 275-284.

Belas, R., Manos, J., & Suvanasuthi, R. (2004). Proteus mirabilis ZapA metalloprotease degrades a broad spectrum of substrates, including antimicrobial peptides. *Infection and Immunity, 72*(9), 5159-5167. doi:10.1128/IAI.72.9.5159-5167.2004

Bergqvist, D., Bronnestam, R., Hedelin, H., & Stahl, A. (1980). The relevance of urinary sampling methods in patients with indwelling Foley catheters. *British Journal of Urology, 52*(2), 92-95.

Bergsten, G., Wullt, B., & Svanborg, C. (2005). Escherichia coli, fimbriae, bacterial persistence and host response induction in the human urinary tract. *International Journal of Medical Microbiology, 295*(6-7), 487-502. doi:DOI: 10.1016/j.ijmm.2005.07.008

Betis, F., Brest, P., Hofman, V., Guignot, J., Bernet-Camard, M. F., Rossi, B., Hofman, P. (2003). The Afa/Dr adhesins of diffusely adhering Escherichia coli stimulate interleukin-8 secretion, activate mitogen-activated protein kinases, and promote polymorphonuclear transepithelial migration in T84 polarized epithelial cells. *Infection and Immunity, 71*(3), 1068-1074.

Biddle, C. (2006). The neurobiology of the human febrile response. *AANA Journal, 74*(2), 145-150.

Bidet, P., Metais, A., Mahjoub-Messai, F., Durand, L., Dehem, M., Aujard, Y., Bonacorsi, S. (2007). Detection and identification by PCR of a highly virulent phylogenetic subgroup among extraintestinal pathogenic Escherichia coli B2 strains. *Applied and Environmental Microbiology, 73*(7), 2373-2377. doi:10.1128/AEM.02341-06

Bingen-Bidois, M., Clermont, O., Bonacorsi, S., Terki, M., Brahimi, N., Loukil, C., Bingen, E. (2002). Phylogenetic analysis and prevalence of urosepsis strains of Escherichia coli bearing pathogenicity island-like domains. *Infection and Immunity, 70*(6), 3216-3226.

Blango, M. G., & Mulvey, M. A. (2010). Persistence of uropathogenic Escherichia coli in the face of multiple antibiotics. *Antimicrobial Agents and Chemotherapy, 54*(5), 1855-1863. doi:10.1128/AAC.00014-10

Blattner, F. R., Plunkett, G., 3rd, Bloch, C. A., Perna, N. T., Burland, V., Riley, M., Shao, Y. (1997). The complete genome sequence of Escherichia coli K-12. *Science (New York, N.Y.), 277*(5331), 1453-1462.

Boen, J. R., Markland, C., & Cass, A. S. (1969). A mathematical comparison of the effects of intermittent and continuous drainage of the bladder on its bacterial count. *Investigative Urology, 6*(4), 383-386.

Bonacorsi, S. P., Clermont, O., Tinsley, C., Le Gall, I., Beaudoin, J. C., Elion, J., Bingen, E. (2000). Identification of regions of the Escherichia coli chromosome specific for neonatal meningitis-associated strains. *Infection and Immunity, 68*(4), 2096-2101.

Boyko, E. J., Fihn, S. D., Scholes, D., Abraham, L., & Monsey, B. (2005). Risk of urinary tract infection and asymptomatic bacteriuria among diabetic and nondiabetic postmenopausal women. *American Journal of Epidemiology, 161*(6), 557-564. doi:10.1093/aje/kwi078

Bremnor, J. D., & Sadovsky, R. (2002). Evaluation of dysuria in adults. *American Family Physician, 65*(8), 1589-1596.

Brooks, G. F., Butel, J. S., & Morse, S. A. (2004). *Jawetz, Melnick, & Adelberg's Medical Microbiology* (23rd ed.). Chicago: Lange Medical Books.

Buckles, E. L., Wang, X., Lane, M. C., Lockatell, C. V., Johnson, D. E., Rasko, D. A., Donnenberg, M. S. (2009). Role of the K2 capsule in Escherichia coli urinary tract infection and serum resistance. *The Journal of Infectious Diseases, 199*(11), 1689-1697. doi:10.1086/598524

Burmolle, M., Bahl, M. I., Jensen, L. B., Sorensen, S. J., & Hansen, L. H. (2008). Type 3 fimbriae, encoded by the conjugative plasmid pOLA52, enhance biofilm formation and transfer frequencies in Enterobacteriaceae strains. *Microbiology (Reading, England), 154*(Pt 1), 187-195. doi:10.1099/mic.0.2007/010454-0

Cade, C. H. (2008). Clinical tools for the assessment of pain in sedated critically ill adults. *Nursing in Critical Care, 13*(6), 288-297. doi:10.1111/j.1478-5153.2008.00294.x

Cashion, A. K., & Cason, C. L. (1984). Accuracy of oral temperatures in intubated patients. *Dimensions of Critical Care Nursing: DCCN, 3*(6), 343-350.

Cerca, N., Jefferson, K. K., Oliveira, R., Pier, G. B., & Azeredo, J. (2006). Comparative antibody-mediated phagocytosis of Staphylococcus epidermidis cells grown in a biofilm or in the planktonic state. *Infection and Immunity, 74*(8), 4849-4855. doi:10.1128/IAI.00230-06

Chow, J. C., Young, D. W., Golenbock, D. T., Christ, W. J., & Gusovsky, F. (1999). Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction. *The Journal of Biological Chemistry, 274*(16), 10689-10692.

Chromek, M., Stankowska, D., Dadfar, E., Kaca, W., Rabbani, H., & Brauner, A. (2005). Interleukin-8 response in cells from the human urinary tract induced by lipopolysaccharides of Proteus mirabilis O3 and O18. *The Journal of Urology, 173*(4), 1381-1384. doi:10.1097/01.ju.0000149032.20713.ed

Clermont, O., Bonacorsi, S., & Bingen, E. (2000). Rapid and simple determination of the Escherichia coli phylogenetic group. *Applied and Environmental Microbiology, 66*(10), 4555-4558.

CMS unveils proposed list of 'no-payment' conditions. (2007). *Healthcare Benchmarks and Quality Improvement, 14*(8), 85-88.

Colodner, R., Eliasberg, T., Chazan, B., & Raz, R. (2006). Clinical significance of bacteriuria with low colony counts of Enterococcus species. *European Journal of Clinical Microbiology & Infectious Diseases: Official Publication of the European Society of Clinical Microbiology, 25*(4), 238-241. doi:10.1007/s10096-006-0132-0

Condron, C., Toomey, D., Casey, R. G., Shaffii, M., Creagh, T., & Bouchier-Hayes, D. (2003). Neutrophil bactericidal function is defective in patients with recurrent urinary tract infections. *Urological Research, 31*(5), 329-334. doi:10.1007/s00240-003-0344-z

Cox, A. J., Hukins, D. W., & Sutton, T. M. (1989). Infection of catheterised patients: bacterial colonisation of encrusted Foley catheters shown by scanning electron microscopy. *Urological Research, 17*(6), 349-352.

Crnich, C. J., & Drinka, P. J. (2007). Does the composition of urinary catheters influence clinical outcomes and the results of research studies? *Infection Control and Hospital Epidemiology: The Official Journal of the Society of Hospital Epidemiologists of America, 28*(1), 102-103. doi:10.1086/510875.

Cunningham, C., Campion, S., Lunnon, K., Murray, C. L., Woods, J. F., Deacon, R. M., Perry, V. H. (2009). Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biological Psychiatry, 65*(4), 304-312. doi:10.1016/j.biopsych.2008.07.024.

Cuthbertson, L., Mainprize, I. L., Naismith, J. H., & Whitfield, C. (2009). Pivotal roles of the outer membrane polysaccharide export and polysaccharide copolymerase protein families in export of extracellular polysaccharides in gram-negative bacteria. *Microbiology and Molecular Biology Reviews: MMBR, 73*(1), 155-177. doi:10.1128/MMBR.00024-08.

Daniels, R., Vanderleyden, J., & Michiels, J. (2004). Quorum sensing and swarming migration in bacteria. *FEMS Microbiology Reviews, 28*(3), 261-289.

Davidoff, R., Yamaguchi, R., Leach, G. E., Park, E., & Lad, P. M. (1997). Multiple urinary cytokine levels of bacterial cystitis. *The Journal of Urology, 157*(5), 1980-1985.

Davis, J. M., Carvalho, H. M., Rasmussen, S. B., & O'Brien, A. D. (2006). Cytotoxic necrotizing factor type 1 delivered by outer membrane vesicles of uropathogenic Escherichia coli attenuates polymorphonuclear leukocyte antimicrobial activity and chemotaxis. *Infection and Immunity, 74*(8), 4401-4408. doi:10.1128/IAI.00637-06.

De Araujo, C., Balestrino, D., Roth, L., Charbonnel, N., & Forestier, C. (2010). Quorum sensing affects biofilm formation through lipopolysaccharide synthesis in Klebsiella pneumoniae. *Research in Microbiology,* doi:10.1016/j.resmic.2010.05.014.

de Man, P., van Kooten, C., Aarden, L., Engberg, I., Linder, H., & Svanborg Eden, C. (1989). Interleukin-6 induced at mucosal surfaces by gram-negative bacterial infection. *Infection and Immunity, 57*(11), 3383-3388.

Deo, S. S., & Vaidya, A. K. (2004). Elevated levels of secretory immunoglobulin A (sIgA) in urinary tract infections. *Indian Journal of Pediatrics, 71*(1), 37-40.

Deville, W. L., Yzermans, J. C., van Duijn, N. P., Bezemer, P. D., van der Windt, D. A., & Bouter, L. M. (2004). The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urology, 4*, 4. doi:10.1186/1471-2490-4-4.

Dhakal, B. K., Kulesus, R. R., & Mulvey, M. A. (2008). Mechanisms and consequences of bladder cell invasion by uropathogenic Escherichia coli. *European Journal of Clinical Investigation, 38 Suppl 2*, 2-11. doi:10.1111/j.1365-2362.2008.01986.x.

Diebold, B. A., & Bokoch, G. M. (2005). Rho GTPases and the control of the oxidative burst in polymorphonuclear leukocytes. *Current Topics in Microbiology and Immunology, 291*, 91-111.

Dinarello, C. A., Cannon, J. G., & Wolff, S. M. (1988). New concepts on the pathogenesis of fever. *Reviews of Infectious Diseases, 10*(1), 168-189.

Domka, J., Lee, J., Bansal, T., & Wood, T. K. (2007). Temporal gene-expression in Escherichia coli K-12 biofilms. *Environmental Microbiology, 9*(2), 332-346. doi:10.1111/j.1462-2920.2006.01143.x.

Donlan, R. M. (2002). Biofilms: microbial life on surfaces. *Emerging Infectious Diseases, 8*(9), 881-890.

Donlan, R. M., & Costerton, J. W. (2002). Biofilms: survival mechanisms of clinically relevant microorganisms. *Clinical Microbiology Reviews, 15*(2), 167-193.

Ducharme, J., Neilson, S., & Ginn, J. L. (2007). Can urine cultures and reagent test strips be used to diagnose urinary tract infection in elderly emergency department patients without focal urinary symptoms? *CJEM : Canadian Journal of Emergency Medical Care = JCMU : Journal Canadien De Soins Medicaux d'Urgence, 9*(2), 87-92.

Duncan, M. J., Li, G., Shin, J. S., Carson, J. L., & Abraham, S. N. (2004). Bacterial penetration of bladder epithelium through lipid rafts. *The Journal of Biological Chemistry, 279*(18), 18944-18951. doi:10.1074/jbc.M400769200.

Dunkelberger, J. R., & Song, W. C. (2010). Complement and its role in innate and adaptive immune responses. *Cell Research, 20*(1), 34-50. doi:10.1038/cr.2009.139.

Eden, B. M., Foreman, M. D., & Sisk, R. (1998). Delirium: comparison of four predictive models in hospitalized critically ill elderly patients. *Applied Nursing Research: ANR, 11*(1), 27-35.

Edwards, J. R., Peterson, K. D., Andrus, M. L., Tolson, J. S., Goulding, J. S., Dudeck, M. A., NHSN Facilities. (2007). National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. *American Journal of Infection Control, 35*(5), 290-301. doi:10.1016/j.ajic.2007.04.001.

Engel, D., Dobrindt, U., Tittel, A., Peters, P., Maurer, J., Gutgemann, I., Kurts, C. (2006). Tumor necrosis factor alpha- and inducible nitric oxide synthase-producing dendritic cells are rapidly recruited to the bladder in urinary tract infection but are dispensable for bacterial clearance. *Infection and Immunity, 74*(11), 6100-6107. doi:10.1128/IAI.00881-06.

Ethel, S., Bhat, G. K., & Hegde, B. M. (2006). Bacterial adherence and humoral immune response in women with symptomatic and asymptomatic urinary tract infection. *Indian Journal of Medical Microbiology, 24*(1), 30-33.

Fabbri, A., Falzano, L., Travaglione, S., Stringaro, A., Malorni, W., Fais, S., & Fiorentini, C. (2002). Rho-activating Escherichia coli cytotoxic necrotizing factor 1: macropinocytosis of apoptotic bodies in human epithelial cells. *International Journal of Medical Microbiology: IJMM, 291*(6-7), 551-554.

Ferrieres, L., Hancock, V., & Klemm, P. (2007). Specific selection for virulent urinary tract infectious Escherichia coli strains during catheter-associated biofilm formation. *FEMS Immunology and Medical Microbiology, 51*(1), 212-219. doi:10.1111/j.1574-695X.2007.00296.x

Feuillet, V., Medjane, S., Mondor, I., Demaria, O., Pagni, P. P., Galan, J. E.,mAlexopoulou, L. (2006). Involvement of Toll-like receptor 5 in the recognition of flagellated bacteria. *Proceedings of the National Academy of Sciences of the United States of America, 103*(33), 12487-12492. doi:10.1073/pnas.0605200103.

Fexby, S., Bjarnsholt, T., Jensen, P. O., Roos, V., Hoiby, N., Givskov, M., & Klemm, P. (2007). Biological Trojan horse: Antigen 43 provides specific bacterial uptake and survival in human neutrophils. *Infection and Immunity, 75*(1), 30-34. doi:10.1128/IAI.01117-06.

Fiorentini, C., & Malorni, W. (2006). Exploiting cell death pathways by an E. coli cytotoxin: autophagy as a double-edged sword for the host. *Autophagy, 2*(4), 310-311.

Fischbach, M. A., Lin, H., Liu, D. R., & Walsh, C. T. (2006). How pathogenic bacteria evade mammalian sabotage in the battle for iron. *Nature Chemical Biology, 2*(3), 132-138. doi:10.1038/nchembio771.

Fliedner, M., Mehls, O., Rauterberg, E. W., & Ritz, E. (1986). Urinary sIgA in children with urinary tract infection. *The Journal of Pediatrics, 109*(3), 416-421.

Floege, J., Boddeker, M., Stolte, H., & Koch, K. M. (1990). Urinary IgA, secretory IgA and secretory component in women with recurrent urinary tract infections. *Nephron, 56*(1), 50-55.

Foster, S. L., & Medzhitov, R. (2009). Gene-specific control of the TLR-induced inflammatory response. *Clinical Immunology (Orlando, Fla.), 130*(1), 7-15. doi:10.1016/j.clim.2008.08.015.

Fowler, C. J., Griffiths, D., & de Groat, W. C. (2008). The neural control of micturition. *Nature Reviews.Neuroscience, 9*(6), 453-466. doi:10.1038/nrn2401.

Foxman, B. (2002). Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *The American Journal of Medicine, 113 Suppl 1A*, 5S-13S.

Frendeus, B., Wachtler, C., Hedlund, M., Fischer, H., Samuelsson, P., Svensson, M., & Svanborg, C. (2001). Escherichia coli P fimbriae utilize the Toll-like receptor 4 pathway for cell activation. *Molecular Microbiology, 40*(1), 37-51.

Gadeholt, H. (1968). Quantitative estimation of cells in urine. An evaluation of the Addis count. *Acta Medica Scandinavica, 183*(4), 369-374.

Gal-Mor, O., & Finlay, B. B. (2006). Pathogenicity islands: a molecular toolbox for bacterial virulence. *Cellular Microbiology, 8*(11), 1707-1719. doi:10.1111/j.1462-5822.2006.00794.x.

Garcia, M. M., Gulati, S., Liepmann, D., Stackhouse, G. B., Greene, K., & Stoller, M. L. (2007). Traditional Foley drainage systems--do they drain the bladder? *The Journal of Urology, 177*(1), 203-7; discussion 207. doi:10.1016/j.juro.2006.08.101.

Garibaldi, R. A., Burke, J. P., Britt, M. R., Miller, M. A., & Smith, C. B. (1980). Meatal colonization and catheter-associated bacteriuria. *The New England Journal of Medicine, 303*(6), 316-318.

Gau, J. T., Shibeshi, M. R., Lu, I. J., Rafique, M., Heh, V., Meyer, D., & Carlsen, W. R. (2009). Interexpert agreement on diagnosis of bacteriuria and urinary tract infection in hospitalized older adults. *The Journal of the American Osteopathic Association, 109*(4), 220-226.

George, J., Bleasdale, S., & Singleton, S. J. (1997). Causes and prognosis of delirium in elderly patients admitted to a district general hospital. *Age and Ageing, 26*(6), 423-427.

Ghenghesh, K. S., Elkateb, E., Berbash, N., Abdel Nada, R., Ahmed, S. F., Rahouma, A., Klena, J. D. (2009). Uropathogens from diabetic patients in Libya: virulence factors and phylogenetic groups of Escherichia coli isolates. *Journal of Medical Microbiology, 58*(Pt 8), 1006-1014. doi:10.1099/jmm.0.007146-0.

Giamboi-Miraglia, A., Travaglione, S., Filippini, P., Fabbri, A., Fiorentini, C., & Falzano, L. (2007). A multinucleating Escherichia coli cytotoxin perturbs cell cycle in cultured epithelial cells. *Toxicology in Vitro: An International Journal Published in Association with BIBRA, 21*(2), 235-239. doi:10.1016/j.tiv.2006.08.013.

Giuliano, K. K., Giuliano, A. J., Scott, S. S., MacLachlan, E., Pysznik, E., Elliot, S., & Woytowicz, D. (2000). Temperature measurement in critically ill adults: a comparison of tympanic and oral methods. *American Journal of Critical Care: An Official Publication, American Association of Critical-Care Nurses, 9*(4), 254-261.

Gobert, A. P., Vareille, M., Glasser, A. L., Hindre, T., de Sablet, T., & Martin, C. (2007). Shiga toxin produced by enterohemorrhagic Escherichia coli inhibits PI3K/NF-kappaB signaling pathway in globotriaosylceramide-3-negative human intestinal epithelial cells. *Journal of Immunology (Baltimore, Md.: 1950), 178*(12), 8168-8174.

Godbout, J. P., Chen, J., Abraham, J., Richwine, A. F., Berg, B. M., Kelley, K. W., & Johnson, R. W. (2005). Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. *The FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 19*(10), 1329-1331. doi:10.1096/fj.05-3776fje.

Goetz, D. H., Holmes, M. A., Borregaard, N., Bluhm, M. E., Raymond, K. N., & Strong, R. K. (2002). The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Molecular Cell, 10*(5), 1033-1043.

Gokula, R. R., Hickner, J. A., & Smith, M. A. (2004). Inappropriate use of urinary catheters in elderly patients at a midwestern community teaching hospital. *American Journal of Infection Control, 32*(4), 196-199. doi:10.1016/j.ajic.2003.08.007.

Golob, J. F.,Jr, Claridge, J. A., Sando, M. J., Phipps, W. R., Yowler, C. J., Fadlalla, A. M., & Malangoni, M. A. (2008). Fever and leukocytosis in critically ill trauma patients: it's not the urine. *Surgical Infections, 9*(1), 49-56. doi:10.1089/sur.2007.023

Goluszko, P., Niesel, D., Nowicki, B., Selvarangan, R., Nowicki, S., Hart, A., Hasan, R. (2001). Dr operon-associated invasiveness of Escherichia coli from pregnant patients with pyelonephritis. *Infection and Immunity, 69*(7), 4678-4680. doi:10.1128/IAI.69.7.4678-4680.2001.

Gonzalez, P. J., Correia, C., Moura, I., Brondino, C. D., & Moura, J. J. (2006). Bacterial nitrate reductases: Molecular and biological aspects of nitrate reduction. *Journal of Inorganic Biochemistry, 100*(5-6), 1015-1023. doi:10.1016/j.jinorgbio.2005.11.024.

Gordon, D. M., Clermont, O., Tolley, H., & Denamur, E. (2008). Assigning Escherichia coli strains to phylogenetic groups: multi-locus sequence typing versus the PCR triplex method. *Environmental Microbiology, 10*(10), 2484-2496. doi:10.1111/j.1462-2920.2008.01669.x.

Graham, J. C., & Galloway, A. (2001). ACP Best Practice No 167: the laboratory diagnosis of urinary tract infection. *Journal of Clinical Pathology, 54*(12), 911-919.

Griebling, T. L. (2005a). Urologic diseases in America project: trends in resource use for urinary tract infections in men. *The Journal of Urology, 173*(4), 1288-1294. doi:10.1097/01.ju.0000155595.98120.8e.

Griebling, T. L. (2005b). Urologic diseases in America project: trends in resource use for urinary tract infections in women. *The Journal of Urology, 173*(4), 1281-1287. doi:10.1097/01.ju.0000155596.98780.82.

Griffin, F. M.,Jr, Griffin, J. A., Leider, J. E., & Silverstein, S. C. (1975). Studies on the mechanism of phagocytosis. I. Requirements for circumferential attachment of particle-bound ligands to specific receptors on the macrophage plasma membrane. *The Journal of Experimental Medicine, 142*(5), 1263-1282.

Grigat, J., Soruri, A., Forssmann, U., Riggert, J., & Zwirner, J. (2007). Chemoattraction of macrophages, T lymphocytes, and mast cells is evolutionarily conserved within the human alpha-defensin family. *Journal of Immunology (Baltimore, Md.: 1950), 179*(6), 3958-3965.

Grinstead, G. F., Scott, R. E., Stevens, B. S., Ward, V. L., & Wilson, D. M. (1987). The Ames Clinitek 200/Multistix 9 urinalysis method compared with manual and microscopic methods. *Clinical Chemistry, 33*(9), 1660-1662.

Gurgoze, M. K., Akarsu, S., Yilmaz, E., Godekmerdan, A., Akca, Z., Ciftci, I., & Aygun, A. D. (2005). Proinflammatory cytokines and procalcitonin in children with acute pyelonephritis. *Pediatric Nephrology (Berlin, Germany), 20*(10), 1445-1448. doi:10.1007/s00467-005-1941-6.

Habler, H. J., Janig, W., & Koltzenburg, M. (1988). A novel type of unmyelinated chemosensitive nociceptor in the acutely inflamed urinary bladder. *Agents and Actions, 25*(3-4), 219-221.

Hacker, J., Blum-Oehler, G., Hochhut, B., & Dobrindt, U. (2003). The molecular basis of infectious diseases: pathogenicity islands and other mobile genetic elements. A review. *Acta Microbiologica Et Immunologica Hungarica, 50*(4), 321-330. doi:10.1556/AMicr.50.2003.4.1.

Hall, G. S., & Woods, G. L. (2007). Medical bacteriology. In R. A. McPherson, & M. R. Pincus (Eds.), *Henry's Clinical Diagnosis and Management by Laboratory Methods* (21st ed.). Philadelphia: Saunders Elsevier.

Han, J. H., Shintani, A., Eden, S., Morandi, A., Solberg, L. M., Schnelle, J., Ely, E. W. (2010). Delirium in the Emergency Department: An Independent Predictor of Death Within 6 Months. *Annals of Emergency Medicine,* doi:10.1016/j.annemergmed.2010.03.003.

Hancock, V., & Klemm, P. (2007). Global gene expression profiling of asymptomatic bacteriuria Escherichia coli during biofilm growth in human urine. *Infection and Immunity, 75*(2), 966-976. doi:10.1128/IAI.01748-06.

Hancock, V., Nielsen, E. M., Krag, L., Engberg, J., & Klemm, P. (2009). Comparative analysis of antibiotic resistance and phylogenetic group patterns in human and porcine urinary tract infectious Escherichia coli. *APMIS: Acta Pathologica, Microbiologica, Et Immunologica Scandinavica, 117*(11), 786-790. doi:10.1111/j.1600-0463.2009.02542.x.

Hancock, V., Seshasayee, A. S., Ussery, D. W., Luscombe, N. M., & Klemm, P. (2008). Transcriptomics and adaptive genomics of the asymptomatic bacteriuria Escherichia coli strain 83972. *Molecular Genetics and Genomics: MGG, 279*(5), 523-534. doi:10.1007/s00438-008-0330-9.

Hasday, J. D., Fairchild, K. D., & Shanholtz, C. (2000). The role of fever in the infected host. *Microbes and Infection / Institut Pasteur, 2*(15), 1891-1904.

Hasler, M. E., & Cohen, J. A. (1982). The effect of oxygen administration on oral temperature assessment. *Nursing Research, 31*(5), 265-268.

Hazelett, S. E., Tsai, M., Gareri, M., & Allen, K. (2006). The association between indwelling urinary catheter use in the elderly and urinary tract infection in acute care. *BMC Geriatrics, 6*, 15. doi:10.1186/1471-2318-6-15.

He, P., Li, N., & Li, S. (2001). A study on beta-lactamase activity of biofilm Escherichia coli. *Zhonghua Jie He He Hu Xi Za Zhi = Zhonghua Jiehe He Huxi Zazhi = Chinese Journal of Tuberculosis and Respiratory Diseases, 24*(9), 537-538.

Hedges, S., Anderson, P., Lidin-Janson, G., de Man, P., & Svanborg, C. (1991). Interleukin-6 response to deliberate colonization of the human urinary tract with gram-negative bacteria. *Infection and Immunity, 59*(1), 421-427.

Heinamaki, P., Haavisto, M., Hakulinen, T., Mattila, K., & Rajala, S. (1986). Mortality in relation to urinary characteristics in the very aged. *Gerontology, 32*(3), 167-171.

Henry, C. J., Huang, Y., Wynne, A. M., & Godbout, J. P. (2009). Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1beta and anti-inflammatory IL-10 cytokines. *Brain, Behavior, and Immunity, 23*(3), 309-317. doi:10.1016/j.bbi.2008.09.002.

Hertting, O., Chromek, M., Slamova, Z., Kadas, L., Soderkvist, M., Vainumae, I., Brauner, A. (2008). Cytotoxic necrotizing factor 1 (CNF1) induces an inflammatory response in the urinary tract in vitro but not in vivo. *Toxicon: Official Journal of the International Society on Toxinology, 51*(8), 1544-1547. doi:10.1016/j.toxicon.2008.03.019.

Herzer, P. J., Inouye, S., Inouye, M., & Whittam, T. S. (1990). Phylogenetic distribution of branched RNA-linked multicopy single-stranded DNA among natural isolates of Escherichia coli. *Journal of Bacteriology, 172*(11), 6175-6181.

Hidron, A. I., Edwards, J. R., Patel, J., Horan, T. C., Sievert, D. M., Pollock, D. A., Participating National Healthcare Safety Network Facilities. (2008). NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infection Control and Hospital Epidemiology: The Official Journal of the Society of Hospital Epidemiologists of America, 29*(11), 996-1011. doi:10.1086/591861.

Hinman, F.,Jr, & Cox, C. E. (1966). The voiding vesical defense mechanism: the mathematical effect of residual urine, voiding interval and volume on bacteriuria. *The Journal of Urology, 96*(4), 491-498.

Hooper, V. D., & Andrews, J. O. (2006). Accuracy of noninvasive core temperature measurement in acutely ill adults: the state of the science. *Biological Research for Nursing, 8*(1), 24-34. doi:10.1177/1099800406289151.

Hooton, T. M., Bradley, S. F., Cardenas, D. D., Colgan, R., Geerlings, S. E., Rice, J. C., Infectious Diseases Society of America. (2010). Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 50*(5), 625-663.

Horan, T. C., Andrus, M., & Dudeck, M. A. (2008). CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. *American Journal of Infection Control, 36*(5), 309-332. doi:DOI: 10.1016/j.ajic.2008.03.002.

Houdouin, V., Bonacorsi, S., Mahjoub-Messai, F., Mariani-Kurkdjian, P., Bidet, P., Sebag, G., Bingen, E. (2007). Phylogenetic groups and virulence factors of Escherichia coli strains causing pyelonephritis in children with and without urinary tract abnormalities. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 13*(7), 740-742. doi:10.1111/j.1469-0691.2007.01748.x.

Hrncir, E. (1996). Mathematical modelling of the concentration of microorganisms in the urinary bladder under simple conditions. *Physiological Research / Academia Scientiarum Bohemoslovaca, 45*(1), 75-82.

Humphreys, H., Newcombe, R. G., Enstone, J., Smyth, E. T., McIlvenny, G., Fitzpatrick, F., Hospital Infection Society Steering Group. (2008). Four country healthcare associated infection prevalence survey 2006: risk factor analysis. *The Journal of Hospital Infection, 69*(3), 249-257. doi:10.1016/j.jhin.2008.04.021.

Hutt, P., Shchepetova, J., Loivukene, K., Kullisaar, T., & Mikelsaar, M. (2006). Antagonistic activity of probiotic lactobacilli and bifidobacteria against entero- and uropathogens. *Journal of Applied Microbiology, 100*(6), 1324-1332. doi:10.1111/j.1365-2672.2006.02857.x.

Inouye, S. K., & Charpentier, P. A. (1996). Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA: The Journal of the American Medical Association, 275*(11), 852-857.

Inouye, S. K., van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P., & Horwitz, R. I. (1990). Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of Internal Medicine, 113*(12), 941-948.

Irwin, D. E., Milsom, I., Hunskaar, S., Reilly, K., Kopp, Z., Herschorn, S., Abrams, P. (2006). Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *European Urology, 50*(6), 1306-14; discussion 1314-5. doi:10.1016/j.eururo.2006.09.019.

Ivanov, A. I., & Romanovsky, A. A. (2004). Prostaglandin E2 as a mediator of fever: synthesis and catabolism. *Frontiers in Bioscience: A Journal and Virtual Library, 9*, 1977-1993.

Jacobi, J., Fraser, G. L., Coursin, D. B., Riker, R. R., Fontaine, D., Wittbrodt, E. T., Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. (2002). Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Critical Care Medicine, 30*(1), 119-141.

Jacobsen, S. M., Stickler, D. J., Mobley, H. L., & Shirtliff, M. E. (2008). Complicated catheter-associated urinary tract infections due to Escherichia coli and Proteus mirabilis. *Clinical Microbiology Reviews, 21*(1), 26-59. doi:10.1128/CMR.00019-07.

Jain, A., Gupta, Y., Agrawal, R., Khare, P., & Jain, S. K. (2007). Biofilms--a microbial life perspective: a critical review. *Critical Reviews in Therapeutic Drug Carrier Systems, 24*(5), 393-443.

Jain, P., Parada, J. P., David, A., & Smith, L. G. (1995). Overuse of the indwelling urinary tract catheter in hospitalized medical patients. *Archives of Internal Medicine, 155*(13), 1425-1429.

Jantausch, B. A., O'Donnell, R., & Wiedermann, B. L. (2000). Urinary interleukin-6 and interleukin-8 in children with urinary tract infection. *Pediatric Nephrology (Berlin, Germany), 15*(3-4), 236-240.

Jaureguy, F., Carbonnelle, E., Bonacorsi, S., Clec'h, C., Casassus, P., Bingen, E., Lortholary, O. (2007). Host and bacterial determinants of initial severity and outcome of Escherichia coli sepsis. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 13*(9), 854-862. doi:10.1111/j.1469-0691.2007.01775.x

Johnson, J. R. (1991). Virulence factors in Escherichia coli urinary tract infection. *Clinical Microbiology Reviews, 4*(1), 80-128.

Johnson, J. R., Murray, A. C., Gajewski, A., Sullivan, M., Snippes, P., Kuskowski, M. A., & Smith, K. E. (2003). Isolation and molecular characterization of nalidixic acid-resistant extraintestinal pathogenic Escherichia coli from retail chicken products. *Antimicrobial Agents and Chemotherapy, 47*(7), 2161-2168.

Johnson, J. R., Scheutz, F., Ulleryd, P., Kuskowski, M. A., O'Bryan, T. T., & Sandberg, T. (2005). Phylogenetic and pathotypic comparison of concurrent urine and rectal Escherichia coli isolates from men with febrile urinary tract infection. *Journal of Clinical Microbiology, 43*(8), 3895-3900. doi:10.1128/JCM.43.8.3895-3900.2005.

Jones, B. V., Mahenthiralingam, E., Sabbuba, N. A., & Stickler, D. J. (2005). Role of swarming in the formation of crystalline Proteus mirabilis biofilms on urinary catheters. *Journal of Medical Microbiology, 54*(Pt 9), 807-813. doi:10.1099/jmm.0.46123-0.

Jones, B. V., Young, R., Mahenthiralingam, E., & Stickler, D. J. (2004). Ultrastructure of Proteus mirabilis swarmer cell rafts and role of swarming in catheter-associated urinary tract infection. *Infection and Immunity, 72*(7), 3941-3950. doi:10.1128/IAI.72.7.3941-3950.2004.

Jorgensen, J. H., & Ferraro, M. J. (2009). Antimicrobial susceptibility testing: a review of general principles and contemporary practices. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 49*(11), 1749-1755. doi:10.1086/647952.

Justice, S. S., Hunstad, D. A., Seed, P. C., & Hultgren, S. J. (2006). Filamentation by Escherichia coli subverts innate defenses during urinary tract infection. *Proceedings of the National Academy of Sciences of the United States of America, 103*(52), 19884-19889. doi:10.1073/pnas.0606329104.

Juthani-Mehta, M., Drickamer, M. A., Towle, V., Zhang, Y., Tinetti, M. E., & Quagliarello, V. J. (2005). Nursing home practitioner survey of diagnostic criteria for urinary tract infections. *Journal of the American Geriatrics Society, 53*(11), 1986-1990. doi:10.1111/j.1532-5415.2005.00470.x.

Juthani-Mehta, M., Tinetti, M., Perrelli, E., Towle, V., Van Ness, P. H., & Quagliarello, V. (2007). Diagnostic accuracy of criteria for urinary tract infection in a cohort of nursing home residents. *Journal of the American Geriatrics Society, 55*(7), 1072-1077. doi:10.1111/j.1532-5415.2007.01217.x.

Kado, C. I. (2009). Horizontal gene transfer: sustaining pathogenicity and optimizing host-pathogen interactions. *Molecular Plant Pathology, 10*(1), 143-150. doi:10.1111/j.1364-3703.2008.00518.x.

Kang, C. I., Chung, D. R., Son, J. S., Ko, K. S., Peck, K. R., Song, J. H., & Korean Network for Study of Infectious Diseases. (2011). Clinical significance of nosocomial acquisition in urinary tract-related bacteremia caused by gram-negative bacilli. *American Journal of Infection Control, 39*(2), 135-140. doi:10.1016/j.ajic.2010.03.022; 10.1016/j.ajic.2010.03.022.

Kang, W. S., Tamarkin, F. J., Wheeler, M. A., & Weiss, R. M. (2004). Rapid up-regulation of endothelial nitric-oxide synthase in a mouse model of Escherichia coli lipopolysaccharide-induced bladder inflammation. *The Journal of Pharmacology and Experimental Therapeutics, 310*(2), 452-458. doi:10.1124/jpet.104.066506.

Kass, E. H. (1956). Asymptomatic infections of the urinary tract. *Transactions of the Association of American Physicians, 69*, 56-64.

Ko, M. C., Liu, C. K., Woung, L. C., Lee, W. K., Jeng, H. S., Lu, S. H., Li, C. Y. (2008). Species and antimicrobial resistance of uropathogens isolated from patients with urinary catheter. *The Tohoku Journal of Experimental Medicine, 214*(4), 311-319.

Komai-Koma, M., Gilchrist, D. S., & Xu, D. (2009). Direct recognition of LPS by human but not murine CD8+ T cells via TLR4 complex. *European Journal of Immunology, 39*(6), 1564-1572. doi:10.1002/eji.200838866.

Kopp, U. C., Cicha, M. Z., Nakamura, K., Nusing, R. M., Smith, L. A., & Hokfelt, T. (2004). Activation of EP4 receptors contributes to prostaglandin E2-mediated stimulation of renal sensory nerves. *American Journal of Physiology.Renal Physiology, 287*(6), F1269-82. doi:10.1152/ajprenal.00230.2004.

Kopp, U. C., Cicha, M. Z., & Smith, L. A. (2002). Endogenous angiotensin modulates PGE(2)-mediated release of substance P from renal mechanosensory nerve fibers. *American Journal of Physiology.Regulatory, Integrative and Comparative Physiology, 282*(1), R19-30.

Koseoglu, H., Aslan, G., Esen, N., Sen, B. H., & Coban, H. (2006). Ultrastructural stages of biofilm development of Escherichia coli on urethral catheters and effects of antibiotics on biofilm formation. *Urology, 68*(5), 942-946. doi:10.1016/j.urology.2006.06.008.

Kristian, S. A., Birkenstock, T. A., Sauder, U., Mack, D., Gotz, F., & Landmann, R. (2008). Biofilm formation induces C3a release and protects Staphylococcus epidermidis from IgG and complement deposition and from neutrophil-dependent killing. *The Journal of Infectious Diseases, 197*(7), 1028-1035. doi:10.1086/528992.

Krzemien, G., Roszkowska-Blaim, M., Kostro, I., Szmigielska, A., Karpinska, M., Sieniawska, M., Toth, K. (2004). Urinary levels of interleukin-6 and interleukin-8 in children with urinary tract infections to age 2. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 10*(11), CR593-7.

Kunin, C. M., White, L. V., & Hua, T. H. (1993). A reassessment of the importance of "low-count" bacteriuria in young women with acute urinary symptoms. *Annals of Internal Medicine, 119*(6), 454-460.

Kupelian, V., Rosen, R. C., Link, C. L., McVary, K. T., Aiyer, L. P., Mollon, P., McKinlay, J. B. (2009). Association of urological symptoms and chronic illness in men and women: contributions of symptom severity and duration--results from the BACH Survey. *The Journal of Urology, 181*(2), 694-700. doi:10.1016/j.juro.2008.10.039.

Kurtzman, E. T., & Buerhaus, P. I. (2008). New Medicare payment rules: danger or opportunity for nursing? *The American Journal of Nursing, 108*(6), 30-35. doi:10.1097/01.NAJ.0000324370.71532.b7.

Kwekkeboom, K. L., & Herr, K. (2001). Assessment of pain in the critically ill. *Critical Care Nursing Clinics of North America, 13*(2), 181-194.

Lammers, R. L., Gibson, S., Kovacs, D., Sears, W., & Strachan, G. (2001). Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. *Annals of Emergency Medicine, 38*(5), 505-512. doi:10.1067/mem.2001.119427.

Landini, P., Antoniani, D., Burgess, J. G., & Nijland, R. (2010). Molecular mechanisms of compounds affecting bacterial biofilm formation and dispersal. *Applied Microbiology and Biotechnology, 86*(3), 813-823. doi:10.1007/s00253-010-2468-8.

Lane, M. C., Lockatell, V., Monterosso, G., Lamphier, D., Weinert, J., Hebel, J. R., Mobley, H. L. (2005). Role of motility in the colonization of uropathogenic Escherichia coli in the urinary tract. *Infection and Immunity, 73*(11), 7644-7656. doi:10.1128/IAI.73.11.7644-7656.2005.

Lane, M. C., & Mobley, H. L. (2007). Role of P-fimbrial-mediated adherence in pyelonephritis and persistence of uropathogenic Escherichia coli (UPEC) in the mammalian kidney. *Kidney International, 72*(1), 19-25. doi:10.1038/sj.ki.5002230.

Latman, N. S. (2003). Clinical thermometry: possible causes and potential solutions to electronic, digital thermometer inaccuracies. *Biomedical Instrumentation & Technology / Association for the Advancement of Medical Instrumentation, 37*(3), 190-196.

Laupland, K. B., Ross, T., Pitout, J. D., Church, D. L., & Gregson, D. B. (2007). Community-onset urinary tract infections: a population-based assessment. *Infection, 35*(3), 150-153. doi:10.1007/s15010-007-6180-2.

Leggett, J. (2008). Approach to fever or suspected infection in the normal host. In L. Goldman, & D. Ausiello (Eds.), *Cecil Medicine* (23rd ed.). Philadelphia: Saunders Elsevier.

Leone, M., Garnier, F., Avidan, M., & Martin, C. (2004). Catheter-associated urinary tract infections in intensive care units. *Microbes and Infection, 6*(11), 1026-1032. doi:DOI: 10.1016/j.micinf.2004.05.016.

Levy, C. R., Eilertsen, T., Kramer, A. M., & Hutt, E. (2006). Which clinical indicators and resident characteristics are associated with health care practitioner nursing home visits or hospital transfer for urinary tract infections? *Journal of the American Medical Directors Association, 7*(8), 493-498. doi:10.1016/j.jamda.2006.03.001.

Ley, K., Laudanna, C., Cybulsky, M. I., & Nourshargh, S. (2007). Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nature Reviews.Immunology, 7*(9), 678-689. doi:10.1038/nri2156.

Li, K., Sacks, S. H., & Sheerin, N. S. (2008). The classical complement pathway plays a critical role in the opsonisation of uropathogenic Escherichia coli. *Molecular Immunology, 45*(4), 954-962. doi:10.1016/j.molimm.2007.07.037.

Liedberg, H. (1989). Catheter induced urethral inflammatory reaction and urinary tract infection. An experimental and clinical study. *Scandinavian Journal of Urology and Nephrology.Supplementum, 124*, 1-43.

Liedberg, H., Ekman, P., & Lundeberg, T. (1990). Pseudomonas aeruginosa: adherence to and growth on different urinary catheter coatings. *International Urology and Nephrology, 22*(5), 487-492.

Lim, S. C., Doshi, V., Castasus, B., Lim, J. K., & Mamun, K. (2006). Factors causing delay in discharge of elderly patients in an acute care hospital. *Annals of the Academy of Medicine, Singapore, 35*(1), 27-32.

Lindsay, D., & von Holy, A. (2006). Bacterial biofilms within the clinical setting: what healthcare professionals should know. *The Journal of Hospital Infection, 64*(4), 313-325. doi:10.1016/j.jhin.2006.06.028.

Lloyd, A. L., Smith, S. N., Eaton, K. A., & Mobley, H. L. (2009). Uropathogenic Escherichia coli Suppresses the host inflammatory response via pathogenicity island genes sisA and sisB. *Infection and Immunity, 77*(12), 5322-5333. doi:10.1128/IAI.00779-09.

Mabbett, A. N., Ulett, G. C., Watts, R. E., Tree, J. J., Totsika, M., Ong, C. L., Schembri, M. A. (2009). Virulence properties of asymptomatic bacteriuria Escherichia coli. *International Journal of Medical Microbiology: IJMM, 299*(1), 53-63. doi:10.1016/j.ijmm.2008.06.003.

Mack, J. M., & Collins, E. M. (2004). Obtaining a residual urine specimen from an indwelling catheter. In G. Altman (Ed.), *Delmar's Fundamental and Advanced Nursing Skills* (2nd ed.) Delmar Cengage Learning.

Mackowiak, P. A., Wasserman, S. S., & Levine, M. M. (1992). A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA: The Journal of the American Medical Association, 268*(12), 1578-1580.

Mackowiak, P. A., & Worden, G. (1994). Carl Reinhold August Wunderlich and the evolution of clinical thermometry. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 18*(3), 458-467.

Macleod, S. M., & Stickler, D. J. (2007). Species interactions in mixed-community crystalline biofilms on urinary catheters. *Journal of Medical Microbiology, 56*(Pt 11), 1549-1557. doi:10.1099/jmm.0.47395-0.

Maclullich, A. M., Ferguson, K. J., Miller, T., de Rooij, S. E., & Cunningham, C. (2008). Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *Journal of Psychosomatic Research, 65*(3), 229-238. doi:10.1016/j.jpsychores.2008.05.019.

Madsen, K. M., Nielsen, S., & Tisher, C. C. (2007). Anatomy of the Kidney. In B. M. Brenner (Ed.), *Brenner & Rector's The Kidney* (8th ed.,). Philadelphia: Saunders Elsevier.

Maroncle, N. M., Sivick, K. E., Brady, R., Stokes, F. E., & Mobley, H. L. (2006). Protease activity, secretion, cell entry, cytotoxicity, and cellular targets of secreted autotransporter toxin of uropathogenic Escherichia coli. *Infection and Immunity, 74*(11), 6124-6134. doi:10.1128/IAI.01086-06.

Martinez, J. J., Mulvey, M. A., Schilling, J. D., Pinkner, J. S., & Hultgren, S. J. (2000). Type 1 pilus-mediated bacterial invasion of bladder epithelial cells. *The EMBO Journal, 19*(12), 2803-2812. doi:10.1093/emboj/19.12.2803

Matsukawa, M., Kunishima, Y., Takahashi, S., Takeyama, K., & Tsukamoto, T. (2005). Bacterial colonization on intraluminal surface of urethral catheter. *Urology, 65*(3), 440-444. doi:10.1016/j.urology.2004.10.065.

McKenzie, S. E., & Schreiber, A. D. (1998). Fc gamma receptors in phagocytes. *Current Opinion in Hematology, 5*(1), 16-21.

McPherson, R., Ben-Ezra, J., & Zhao, S. (2006). Basic examination of the urine. In R. A. McPherson, & M. R. Pincus (Eds.), *Henry's Clinical Diagnosis and Management by Laboratory Methods* (21st ed.,). St. Louis, Missouri: W.B. Saunders.

Meagher, D. J., Maclullich, A. M., & Laurila, J. V. (2008). Defining delirium for the International Classification of Diseases, 11th Revision. *Journal of Psychosomatic Research, 65*(3), 207-214. doi:10.1016/j.jpsychores.2008.05.015.

Medina-Bombardo, D., Segui-Diaz, M., Roca-Fusalba, C., Llobera, J., & dysuria team. (2003). What is the predictive value of urinary symptoms for diagnosing urinary tract infection in women? *Family Practice, 20*(2), 103-107.

Meerabeau, L. (1999). The management of embarrassment and sexuality in health care. *Journal of Advanced Nursing, 29*(6), 1507-1513.

Merz, A. J., & Forest, K. T. (2002). Bacterial surface motility: slime trails, grappling hooks and nozzles. *Current Biology: CB, 12*(8), R297-303.

Meyrier, A., & Zalaznik, D. (2006). *Urine sampling and culture in the diagnosis of urinary tract infection in adults.*

Midthun, S. J. (2004). Criteria for urinary tract infection in the elderly: variables that challenge nursing assessment. *Urologic Nursing: Official Journal of the American Urological Association Allied, 24*(3), 157-62, 166-9, 186; quiz 170.

Milan, P. B., & Ivan, I. M. (2009). Catheter-associated and nosocomial urinary tract infections: antibiotic resistance and influence on commonly used antimicrobial therapy. *International Urology and Nephrology, 41*(3), 461-464. doi:10.1007/s11255-008-9468-y; 10.1007/s11255-008-9468-y.

Miller, D. J., Yoshikawa, T. T., & Norman, D. C. (1995). Effect of age on fever response to recombinant interleukin-6 in a murine model. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 50*(5), M276-9.

Miller, D. C., Saigal, C. S., & Litwin, M. S. (2009). The Demographic Burden of Urologic Diseases in America. *Urologic Clinics of North America, 36*(1), 11-27. doi:DOI: 10.1016/j.ucl.2008.08.004.

Mills, M., Meysick, K. C., & O'Brien, A. D. (2000). Cytotoxic necrotizing factor type 1 of uropathogenic Escherichia coli kills cultured human uroepithelial 5637 cells by an apoptotic mechanism. *Infection and Immunity, 68*(10), 5869-5880.

Miraglia, A. G., Travaglione, S., Meschini, S., Falzano, L., Matarrese, P., Quaranta, M. G., Fabbri, A. (2007). Cytotoxic necrotizing factor 1 prevents apoptosis via the Akt/IkappaB kinase pathway: role of nuclear factor-kappaB and Bcl-2. *Molecular Biology of the Cell, 18*(7), 2735-2744. doi:10.1091/mbc.E06-10-0910.

Monane, M., Gurwitz, J. H., Lipsitz, L. A., Glynn, R. J., Choodnovskiy, I., & Avorn, J. (1995). Epidemiologic and diagnostic aspects of bacteriuria: a longitudinal study in older women. *Journal of the American Geriatrics Society, 43*(6), 618-622.

Montalvo, J. A., Acosta, J. A., Rodriguez, P., Hatzigeorgiou, C., Gonzalez, B., & Calderin, A. R. (2006). Factors associated with mortality in critically injured trauma patients who require simultaneous cultures. *Surgical Infections, 7*(2), 137-142. doi:10.1089/sur.2006.7.137.

Moore, E. E., Jackson, S. L., Boyko, E. J., Scholes, D., & Fihn, S. D. (2008). Urinary incontinence and urinary tract infection: temporal relationships in postmenopausal women. *Obstetrics and Gynecology, 111*(2 Pt 1), 317-323. doi:10.1097/AOG.0b013e318160d64a.

Moran, D. S., & Mendal, L. (2002). Core temperature measurement: methods and current insights. *Sports Medicine (Auckland, N.Z.), 32*(14), 879-885.

Moreno, E., Andreu, A., Perez, T., Sabate, M., Johnson, J. R., & Prats, G. (2006). Relationship between Escherichia coli strains causing urinary tract infection in women and the dominant faecal flora of the same hosts. *Epidemiology and Infection, 134*(5), 1015-1023. doi:10.1017/S0950268806005917.

Moreno, E., Andreu, A., Pigrau, C., Kuskowski, M. A., Johnson, J. R., & Prats, G. (2008). Relationship between Escherichia coli strains causing acute cystitis in women and the fecal E. coli population of the host. *Journal of Clinical Microbiology, 46*(8), 2529-2534. doi:10.1128/JCM.00813-08.

Moreno, E., Johnson, J. R., Perez, T., Prats, G., Kuskowski, M. A., & Andreu, A. (2009). Structure and urovirulence characteristics of the fecal Escherichia coli population among healthy women. *Microbes and Infection / Institut Pasteur, 11*(2), 274-280. doi:10.1016/j.micinf.2008.12.002.

Morozkina, E. V., & Zvyagilskaya, R. A. (2007). Nitrate reductases: structure, functions, and effect of stress factors. *Biochemistry.Biokhimiia, 72*(10), 1151-1160.

Mossman, K. L., Mian, M. F., Lauzon, N. M., Gyles, C. L., Lichty, B., Mackenzie, R., Ashkar, A. A. (2008). Cutting edge: FimH adhesin of type 1 fimbriae is a novel TLR4 ligand. *Journal of Immunology (Baltimore, Md.: 1950), 181*(10), 6702-6706.

Moxnes, J. F., & Hausken, K. (2006). A mathematical model for the proliferation of bacteria in the urinary bladder due to enlarged prostate. *Medical Hypotheses, 67*(6), 1391-1399. doi:10.1016/j.mehy.2006.05.049.

Muller, W. A. (2002). Leukocyte-endothelial cell interactions in the inflammatory response. *Laboratory Investigation; a Journal of Technical Methods and Pathology, 82*(5), 521-533.

Muller, W. A. (2003). Leukocyte-endothelial-cell interactions in leukocyte transmigration and the inflammatory response. *Trends in Immunology, 24*(6), 327-334.

Nacey, J. N., Delahunt, B., & Tulloch, A. G. (1985). The assessment of catheter-induced urethritis using an experimental dog model. *The Journal of Urology, 134*(3), 623-625.

National Healthcare Safety Network. (2010). NHSN Patient Safety Component Manual. Retrieved July 27, 2010, from http://www.cdc.gov/nhsn/TOC_PSCManual.html.

Nauseef, W. M., & Clark, R. A. (2009). Granulocytic phagocytes. In G. L. Mandell, J. E. Bennett & R. Dolin (Eds.), *Mandell, Douglas, & Bennett's Principles and Practice of Infectious Diseases* (7th ed.,). Philadelphia: Churchill Livingstone Elsevier.

Nauseef, W. M. (2008). Biological roles for the NOX family NADPH oxidases. *The Journal of Biological Chemistry, 283*(25), 16961-16965. doi:10.1074/jbc.R700045200.

Nazareth, H., Genagon, S. A., & Russo, T. A. (2007). Extraintestinal pathogenic Escherichia coli survives within neutrophils. *Infection and Immunity, 75*(6), 2776-2785. doi:10.1128/IAI.01095-06.

Nicholson, T. F., Watts, K. M., & Hunstad, D. A. (2009). OmpA of uropathogenic Escherichia coli promotes postinvasion pathogenesis of cystitis. *Infection and Immunity, 77*(12), 5245-5251. doi:10.1128/IAI.00670-09.

Nicolle, L. E. (2005). Catheter-related urinary tract infection. *Drugs & Aging, 22*(8), 627-639.

Nicolle, L. E., Bjornson, J., Harding, G. K., & MacDonell, J. A. (1983). Bacteriuria in elderly institutionalized men. *The New England Journal of Medicine, 309*(23), 1420-1425.

Nicolle, L. E., & Brunka, J. (1990). Urinary IgG and IgA antibodies in elderly individuals with bacteriuria. *Gerontology, 36*(5-6), 345-355.

Nicolle, L. E., Brunka, J., Orr, P., Wilkins, J., & Harding, G. K. (1993). Urinary immunoreactive interleukin-1 alpha and interleukin-6 in bacteriuric institutionalized elderly subjects. *The Journal of Urology, 149*(5), 1049-1053.

Nicolle, L. E., Mayhew, W. J., & Bryan, L. (1987). Prospective randomized comparison of therapy and no therapy for asymptomatic bacteriuria in institutionalized elderly women. *The American Journal of Medicine, 83*(1), 27-33.

Nicolle, L., Bradley, S., Colgan, R., Rice, J., Schaeffer, A., & Hooton, T. (2005). Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. *Clinical Infectious Diseases, 40*(5), 643-654.

Nordenstam, G. R., Brandberg, C. A., Oden, A. S., Svanborg Eden, C. M., & Svanborg, A. (1986). Bacteriuria and mortality in an elderly population. *The New England Journal of Medicine, 314*(18), 1152-1156.

Nordling, L., Lundeberg, T., Ekman, P., Liedberg, H., & Theodorsson, E. (1992). Role of the autonomic nervous system in catheter-induced urethral inflammation. *European Urology, 21*(4), 328-331.

Norman, D. C. (2000). Fever in the elderly. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 31*(1), 148-151. doi:10.1086/313896

Nowicki, B., Selvarangan, R., & Nowicki, S. (2001). Family of Escherichia coli Dr Adhesins: Decay□Accelerating Factor Receptor Recognition and Invasiveness. *The Journal of Infectious Diseases, 183*, S24-S27.

Nys, S., van Merode, T., Bartelds, A. I., & Stobberingh, E. E. (2006). Urinary tract infections in general practice patients: diagnostic tests versus bacteriological culture. *The Journal of Antimicrobial Chemotherapy, 5*7(5), 955-958. doi:10.1093/jac/dkl082

Oelschlaeger, T. A., Dobrindt, U., & Hacker, J. (2002). Virulence factors of uropathogens. *Current Opinion in Urology, 1*2(1), 33-38.

Olsson, L. E., Wheeler, M. A., Sessa, W. C., & Weiss, R. M. (1998). Bladder instillation and intraperitoneal injection of Escherichia coli lipopolysaccharide up-regulate cytokines and iNOS in rat urinary bladder. *The Journal of Pharmacology and Experimental Therapeutics, 28*4(3), 1203-1208.

Ong, C. L., Beatson, S. A., McEwan, A. G., & Schembri, M. A. (2009). Conjugative plasmid transfer and adhesion dynamics in an Escherichia coli biofilm. *Applied and Environmental Microbiology, 7*5(21), 6783-6791. doi:10.1128/AEM.00974-09.

Orr, P. H., Nicolle, L. E., Duckworth, H., Brunka, J., Kennedy, J., Murray, D., & Harding, G. K. (1996). Febrile urinary infection in the institutionalized elderly. *The American Journal of Medicine, 10*0(1), 71-77.

Orskov, F. (1978). Virulence factors of the bacterial cell surface. *The Journal of Infectious Diseases, 13*7(5), 630-633.

Otto, G., Burdick, M., Strieter, R., & Godaly, G. (2005). Chemokine response to febrile urinary tract infection. *Kidney International, 6*8(1), 62-70. doi:10.1111/j.1523-1755.2005.00381.x.

Ouslander, J. G., Schapira, M., Schnelle, J. F., Uman, G., Fingold, S., Tuico, E., & Nigam, J. G. (1995). Does eradicating bacteriuria affect the severity of chronic urinary incontinence in nursing home residents*? Annals of Internal Medicine, 12*2(10), 749-754.

Parsek, M. R., & Greenberg, E. P. (2005). Sociomicrobiology: the connections between quorum sensing and biofilms. *Trends in Microbiology, 1*3(1), 27-33. doi:10.1016/j.tim.2004.11.007.

Parsons, C. L., Greenberger, M., Gabal, L., Bidair, M., & Barme, G. (1998). The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *The Journal of Urology, 15*9(6), 1862-6; discussion 1866-7.

Pezzlo, M. (1988). Detection of urinary tract infections by rapid methods. *Clinical Microbiology Reviews,* 1(3), 268-280.

Piatti, G., Mannini, A., Balistreri, M., & Schito, A. M. (2008). Virulence factors in urinary Escherichia coli strains: phylogenetic background and quinolone and fluoroquinolone resistance. *Journal of Clinical Microbiology, 4*6(2), 480-487. doi:10.1128/JCM.01488-07.

Piccoli, G. B., Consiglio, V., Colla, L., Mesiano, P., Magnano, A., Burdese, M., Piccoli, G. (2006). Antibiotic treatment for acute 'uncomplicated' or 'primary' pyelonephritis: a systematic, 'semantic revision'. *International Journal of Antimicrobial Agents, 28 Suppl* 1, S49-63. doi:10.1016/j.ijantimicag.2006.05.017.

Platt, R. (1983). Quantitative definition of bacteriuria. *The American Journal of Medicine, 75*(1B), 44-52.

Pollock, H. M. (1983). Laboratory techniques for detection of urinary tract infection and assessment of value. *The American Journal of Medicine, 75*(1B), 79-84.

Raffi, H. S., Bates, J. M., Jr., Laszik, Z., & Kumar, S. (2005). Tamm-Horsfall protein acts as a general host-defense factor against bacterial cystitis. *American Journal of Nephrology, 25*(6), 570-578. doi:10.1159/000088990.

Ragnarsdottir, B., Fischer, H., Godaly, G., Gronberg-Hernandez, J., Gustafsson, M., Karpman, D., Svanborg, C. (2008). TLR- and CXCR1-dependent innate immunity: insights into the genetics of urinary tract infections. *European Journal of Clinical Investigation, 38 Suppl* 2, 12-20. doi:10.1111/j.1365-2362.2008.02004.x.

Rahkonen, T., Makela, H., Paanila, S., Halonen, P., Sivenius, J., & Sulkava, R. (2000). Delirium in elderly people without severe predisposing disorders: etiology and 1-year prognosis after discharge. *International Psychogeriatrics / IPA, 12*(4), 473-481.

Ratliff, T. L. (2005). Tamm-Horsfall glycoprotein links innate immune cell activation with adaptive immunity via a toll-like receptor-4-dependent mechanism. *The Journal of Urology, 174*(3), 1150.

Razatos, A., Ong, Y. L., Sharma, M. M., & Georgiou, G. (1998). Molecular determinants of bacterial adhesion monitored by atomic force microscopy. *Proceedings of the National Academy of Sciences of the United States of America, 95*(19), 11059-11064.

Real, J. M., Munro, P., Buisson-Touati, C., Lemichez, E., Boquet, P., & Landraud, L. (2007). Specificity of immunomodulator secretion in urinary samples in response to infection by alpha-hemolysin and CNF1 bearing uropathogenic Escherichia coli. *Cytokine, 37*(1), 22-25. doi:10.1016/j.cyto.2007.02.016.

Relman, D. A., & Falkow, S. (2005). A molecular perspective of microbial pathogenicity. In G. L. Mandell, J. E. Bennett & R. Dolin (Eds.), *Principles and Practice of Infectious Disease* (6th ed.,). Orlando, Florida: Churchill Livingstone.

Restieri, C., Garriss, G., Locas, M. C., & Dozois, C. M. (2007). Autotransporter-encoding sequences are phylogenetically distributed among Escherichia coli clinical isolates and reference strains. *Applied and Environmental Microbiology, 73*(5), 1553-1562. doi:10.1128/AEM.01542-06.

Ribera, M. C., Pascual, R., Orozco, D., Perez Barba, C., Pedrera, V., & Gil, V. (2006). Incidence and risk factors associated with urinary tract infection in diabetic patients with and without asymptomatic bacteriuria. *European Journal of Clinical Microbiology & Infectious Diseases: Official Publication of the European Society of Clinical Microbiology, 25*(6), 389-393. doi:10.1007/s10096-006-0148-5.

Rice, J. C., Peng, T., Spence, J. S., Wang, H., Goldblum, R. M., Corthesy, B., & Nowicki, B. J. (2005). Pyelonephritic Escherichia coli Expressing P Fimbriae Decrease Immune Response of the Mouse Kidney. *Journal of the American Society of Nephrology, 16*(12), 3583-3591. doi:10.1681/ASN.2005030243.

Riedasch, G., Heck, P., Rauterberg, E., & Ritz, E. (1983). Does low urinary sIgA predispose to urinary tract infection? *Kidney International, 23*(5), 759-763.

Rocha, S. P., Pelayo, J. S., & Elias, W. P. (2007). Fimbriae of uropathogenic Proteus mirabilis. *FEMS Immunology and Medical Microbiology, 51*(1), 1-7. doi:10.1111/j.1574-695X.2007.00284.x.

Rodhe, N., Lofgren, S., Matussek, A., Andre, M., Englund, L., Kuhn, I., & Molstad, S. (2008). Asymptomatic bacteriuria in the elderly: high prevalence and high turnover of strains. *Scandinavian Journal of Infectious Diseases, 40*(10), 804-810. doi:10.1080/00365540802195242.

Rodhe, N., Lofgren, S., Strindhall, J., Matussek, A., & Molstad, S. (2009). Cytokines in urine in elderly subjects with acute cystitis and asymptomatic bacteriuria. *Scandinavian Journal of Primary Health Care,* 1-6. doi:10.1080/02813430902757634.

Rodhe, N., Molstad, S., Englund, L., & Svardsudd, K. (2006). Asymptomatic bacteriuria in a population of elderly residents living in a community setting: prevalence, characteristics and associated factors. *Family Practice, 23*(3), 303-307. doi:10.1093/fampra/cml007.

Rodriguez, L. M., Robles, B., Marugan, J. M., Suarez, A., & Santos, F. (2008). Urinary interleukin-6 is useful in distinguishing between upper and lower urinary tract infections. *Pediatric Nephrology (Berlin, Germany), 23*(3), 429-433. doi:10.1007/s00467-007-0670-4.

Roos, V., Ulett, G. C., Schembri, M. A., & Klemm, P. (2006). The asymptomatic bacteriuria Escherichia coli strain 83972 outcompetes uropathogenic E. coli strains in human urine. *Infection and Immunity, 74*(1), 615-624. doi:10.1128/IAI.74.1.615-624.2006.

Rudick, C. N., Billips, B. K., Pavlov, V. I., Yaggie, R. E., Schaeffer, A. J., & Klumpp, D. J. (2010). Host-pathogen interactions mediating pain of urinary tract infection. *The Journal of Infectious Diseases, 201*(8), 1240-1249. doi:10.1086/651275.

Rudolph, J. L., Inouye, S. K., Jones, R. N., Yang, F. M., Fong, T. G., Levkoff, S. E., & Marcantonio, E. R. (2010). Delirium: an independent predictor of functional decline after cardiac surgery. *Journal of the American Geriatrics Society, 58*(4), 643-649. doi:10.1111/j.1532-5415.2010.02762.x.

Russo, T. A., & Carlino-MacDonald, U. (2008). Extraintestinal pathogenic isolates of Escherichia coli do not possess active IgA1, IgA2, sIgA or IgG proteases. *FEMS Immunology and Medical Microbiology, 53*(1), 65-71. doi:10.1111/j.1574-695X.2008.00393.x.

Russo, T. A., & Johnson, J. R. (2003). Medical and economic impact of extraintestinal infections due to Escherichia coli: focus on an increasingly important endemic problem. *Microbes and Infection / Institut Pasteur, 5*(5), 449-456.

Russo, T. A., McFadden, C. D., Carlino-MacDonald, U. B., Beanan, J. M., Barnard, T. J., & Johnson, J. R. (2002). IroN functions as a siderophore receptor and is a urovirulence factor in an extraintestinal pathogenic isolate of Escherichia coli. *Infection and Immunity, 70*(12), 7156-7160.

Sabbuba, N., Hughes, G., & Stickler, D. J. (2002). The migration of Proteus mirabilis and other urinary tract pathogens over Foley catheters. *BJU International, 89*(1), 55-60.

Saemann, M. D., Weichhart, T., Zeyda, M., Staffler, G., Schunn, M., Stuhlmeier, K. M., Zlabinger, G. J. (2005). Tamm-Horsfall glycoprotein links innate immune cell activation with adaptive immunity via a Toll-like receptor-4-dependent mechanism. *The Journal of Clinical Investigation, 115*(2), 468-475. doi:10.1172/JCI22720.

Saint, S. (2000a). How to prevent urinary catheter-related infections in the critically ill: Recognizing when indwelling devices must be used and when they should not. *The Journal of Critical Illness, 15*(8), 419-423.

Saint, S. (2000b). Clinical and economic consequences of nosocomial catheter-related bacteriuria. *American Journal of Infection Control, 28*(1), 68-75.

Saint, S., & Chenoweth, C. E. (2003). Biofilms and catheter-associated urinary tract infections. *Infectious Disease Clinics of North America, 17*(2), 411-432.

Saint, S., Kaufman, S. R., Rogers, M. A., Baker, P. D., Boyko, E. J., & Lipsky, B. A. (2006). Risk factors for nosocomial urinary tract-related bacteremia: a case-control study. *American Journal of Infection Control, 34*(7), 401-407. doi:10.1016/j.ajic.2006.03.001.

Saint, S., Lipsky, B. A., & Goold, S. D. (2002). Indwelling urinary catheters: a one-point restraint? *Annals of Internal Medicine, 137*(2), 125-127.

Samuelsson, P., Hang, L., Wullt, B., Irjala, H., & Svanborg, C. (2004). Toll-like receptor 4 expression and cytokine responses in the human urinary tract mucosa. *Infection and Immunity, 72*(6), 3179-3186. doi:10.1128/IAI.72.6.3179-3186.2004.

Savill, J. S., Wyllie, A. H., Henson, J. E., Walport, M. J., Henson, P. M., & Haslett, C. (1989). Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. *The Journal of Clinical Investigation, 83*(3), 865-875. doi:10.1172/JCI113970.

Schembri, M. A., Kjaergaard, K., & Klemm, P. (2003). Global gene expression in Escherichia coli biofilms. *Molecular Microbiology, 48*(1), 253-267.

Schoor, R. A., Anderson, B., Klumpp, D. J., & Schaeffer, A. J. (2001). Secretory IGA differentially promotes adherence of type 1-piliated Escherichia coli to immortalized vaginal epithelial cell lines. *Urology, 57*(3), 556-561.

Sebag, J., Reed, W. P., & Williams, R. C.,Jr. (1977). Effect of temperature on bacterial killing by serum and by polymorphonuclear leukocytes. *Infection and Immunity, 16*(3), 947-954.

Selander, R. K., Musser, J. M., Caugant, D. A., Gilmour, M. N., & Whittam, T. S. (1987). Population genetics of pathogenic bacteria. *Microbial Pathogenesis, 3*(1), 1-7.

Selvarangan, R., Goluszko, P., Singhal, J., Carnoy, C., Moseley, S., Hudson, B., Nowicki, B. (2004). Interaction of Dr adhesin with collagen type IV is a critical step in Escherichia coli renal persistence. *Infection and Immunity, 72*(8), 4827-4835. doi:10.1128/IAI.72.8.4827-4835.2004.

Sengelov, H. (1995). Complement receptors in neutrophils. *Critical Reviews in Immunology, 15*(2), 107-131.

Serafini-Cessi, F., Malagolini, N., & Cavallone, D. (2003). Tamm-Horsfall glycoprotein: biology and clinical relevance. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation, 42*(4), 658-676.

Shea, V. K., Cai, R., Crepps, B., Mason, J. L., & Perl, E. R. (2000). Sensory fibers of the pelvic nerve innervating the Rat's urinary bladder. *Journal of Neurophysiology, 84*(4), 1924-1933.

Sheu, J. N., Chen, M. C., Lue, K. H., Cheng, S. L., Lee, I. C., Chen, S. M., & Tsay, G. J. (2006). Serum and urine levels of interleukin-6 and interleukin-8 in children with acute pyelonephritis. *Cytokine, 36*(5-6), 276-282. doi:10.1016/j.cyto.2007.02.006.

Sivick, K. E., Schaller, M. A., Smith, S. N., & Mobley, H. L. (2010). The innate immune response to uropathogenic Escherichia coli involves IL-17A in a murine model of urinary tract infection. *Journal of Immunology (Baltimore, Md.: 1950), 184*(4), 2065-2075. doi:10.4049/jimmunol.0902386

Smith, S. P., Manges, A. R., & Riley, L. W. (2008). Temporal changes in the prevalence of community-acquired antimicrobial-resistant urinary tract infection affected by Escherichia coli clonal group composition. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 46*(5), 689-695. doi:10.1086/527386.

Smith, Y. C., Rasmussen, S. B., Grande, K. K., Conran, R. M., & O'Brien, A. D. (2008). Hemolysin of uropathogenic Escherichia coli evokes extensive shedding of the uroepithelium and hemorrhage in bladder tissue within the first 24 hours after intraurethral inoculation of mice. *Infection and Immunity, 76*(7), 2978-2990. doi:10.1128/IAI.00075-08.

Snyder, J. A., Haugen, B. J., Buckles, E. L., Lockatell, C. V., Johnson, D. E., Donnenberg, M. S., Mobley, H. L. (2004). Transcriptome of uropathogenic Escherichia coli during urinary tract infection. *Infection and Immunity, 72*(11), 6373-6381. doi:10.1128/IAI.72.11.6373-6381.2004.

Snyder, J. A., Haugen, B. J., Lockatell, C. V., Maroncle, N., Hagan, E. C., Johnson, D. E., Mobley, H. L. (2005). Coordinate expression of fimbriae in uropathogenic Escherichia coli. *Infection and Immunity, 73*(11), 7588-7596. doi:10.1128/IAI.73.11.7588-7596.2005.

Soderblom, T., Oxhamre, C., Torstensson, E., & Richter-Dahlfors, A. (2003). Bacterial protein toxins and inflammation. *Scandinavian Journal of Infectious Diseases, 35*(9), 628-631.

Soja, S. L., Pandharipande, P. P., Fleming, S. B., Cotton, B. A., Miller, L. R., Weaver, S. G., Ely, E. W. (2008). Implementation, reliability testing, and compliance monitoring of the Confusion Assessment Method for the Intensive Care Unit in trauma patients. *Intensive Care Medicine, 34*(7), 1263-1268. doi:10.1007/s00134-008-1031-x.

Soruri, A., Grigat, J., Forssmann, U., Riggert, J., & Zwirner, J. (2007). beta-Defensins chemoattract macrophages and mast cells but not lymphocytes and dendritic cells: CCR6 is not involved. *European Journal of Immunology, 37*(9), 2474-2486. doi:10.1002/eji.200737292.

Sparkman, N. L., & Johnson, R. W. (2008). Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. *Neuroimmunomodulation, 15*(4-6), 323-330. doi:10.1159/000156474.

St John, A., Boyd, J. C., Lowes, A. J., & Price, C. P. (2006). The use of urinary dipstick tests to exclude urinary tract infection: a systematic review of the literature. *American Journal of Clinical Pathology, 126*(3), 428-436. doi:10.1309/C69RW1BT7E4QAFPV.

Stamm, W. E. (1988). Protocol for diagnosis of urinary tract infection: reconsidering the criterion for significant bacteriuria. *Urology, 32*(2 Suppl), 6-12.

Stamm, W. E. (1992). Criteria for the diagnosis of urinary tract infection and for the assessment of therapeutic effectiveness. *Infection, 20 Suppl 3*, S151-4; discussion S160-1.

Steiner, A. A., Ivanov, A. I., Serrats, J., Hosokawa, H., Phayre, A. N., Robbins, J. R., Romanovsky, A. A. (2006). Cellular and molecular bases of the initiation of fever. *PLoS Biology, 4*(9), e284. doi:10.1371/journal.pbio.0040284.

Stern, J. A., Hsieh, Y., & Schaeffer, A. J. (2004). Residual Urine in an Elderly Female Population: Novel Implications for Oral Estrogen Replacement and Impact on Recurrent Urinary Tract Infection. *The Journal of Urology, 171*(2, Part 1), 768-770. doi:DOI: 10.1097/01.ju.0000107261.64927.b3

Stickler, D., Young, R., Jones, G., Sabbuba, N., & Morris, N. (2003). Why are Foley catheters so vulnerable to encrustation and blockage by crystalline bacterial biofilm? *Urological Research, 31*(5), 306-311. doi:10.1007/s00240-003-0340-3.

Stickler, D. J. (2002). Susceptibility of antibiotic-resistant gram-negative bacteria to biocides: a perspective from the study of catheter biofilms. *Symposium Series (Society for Applied Microbiology), (31)*(31), 163S-170S.

Stickler, D. J., Lear, J. C., Morris, N. S., Macleod, S. M., Downer, A., Cadd, D. H., & Feast, W. J. (2006). Observations on the adherence of Proteus mirabilis onto polymer surfaces. *Journal of Applied Microbiology, 100*(5), 1028-1033. doi:10.1111/j.1365-2672.2006.02840.x.

Stickler, D. J., & Morgan, S. D. (2008). Observations on the development of the crystalline bacterial biofilms that encrust and block Foley catheters. *The Journal of Hospital Infection, 69*(4), 350-360. doi:10.1016/j.jhin.2008.04.031.

Svanborg, C., Bergsten, G., Fischer, H., Frendeus, B., Godaly, G., Gustafsson, E., Wullt, B. (2001). The 'innate' host response protects and damages the infected urinary tract. *Annals of Medicine, 33*(9), 563-570.

Svanborg, C., Bergsten, G., Fischer, H., Godaly, G., Gustafsson, M., Karpman, D., Wullt, B. (2006). Uropathogenic Escherichia coli as a model of host-parasite interaction. *Current Opinion in Microbiology, 9*(1), 33-39. doi:10.1016/j.mib.2005.12.012.

Svanborg-Eden, C., & Svennerholm, A. M. (1978). Secretory immunoglobulin A and G antibodies prevent adhesion of Escherichia coli to human urinary tract epithelial cells. *Infection and Immunity, 22*(3), 790-797.

Swanson, J. A. (2008). Shaping cups into phagosomes and macropinosomes. *Nature Reviews.Molecular Cell Biology, 9*(8), 639-649. doi:10.1038/nrm2447.

Takeuchi, O., Takeda, K., Hoshino, K., Adachi, O., Ogawa, T., & Akira, S. (2000). Cellular responses to bacterial cell wall components are mediated through MyD88-dependent signaling cascades. *International Immunology, 12*(1), 113-117.

Tambyah, P. A., Knasinski, V., & Maki, D. G. (2002). The direct costs of nosocomial catheter-associated urinary tract infection in the era of managed care. *Infection Control and Hospital Epidemiology: The Official Journal of the Society of Hospital Epidemiologists of America, 23*(1), 27-31. doi:10.1086/501964.

Tambyah, P. A., & Maki, D. G. (2000a). Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. *Archives of Internal Medicine, 160*(5), 678-682.

Tambyah, P. A., & Maki, D. G. (2000b). The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. *Archives of Internal Medicine, 160*(5), 673-677.

Tiba, M. R., Yano, T., & Leite, D. d. S. (2008). Genotypic characterization of virulence factors in Escherichia coli strains from patients with cystitis. *Revista do Instituto De Medicina Tropical De São Paulo, 50*(5), 255-260.

Trautner, B. W., & Darouiche, R. O. (2004). Role of biofilm in catheter-associated urinary tract infection. *American Journal of Infection Control, 32*(3), 177-183. doi:10.1016/j.ajic.2003.08.005

Trautner, B. W., Hull, R. A., Thornby, J. I., & Darouiche, R. O. (2007). Coating urinary catheters with an avirulent strain of Escherichia coli as a means to establish asymptomatic colonization. *Infection Control and Hospital Epidemiology: The Official Journal of the Society of Hospital Epidemiologists of America, 28*(1), 92-94. doi:10.1086/510872.

Truzzi, J. C., Almeida, F. M., Nunes, E. C., & Sadi, M. V. (2008). Residual urinary volume and urinary tract infection--when are they linked? *The Journal of Urology, 180*(1), 182-185. doi:10.1016/j.juro.2008.03.044.

Tsuchida, T., Makimoto, K., Ohsako, S., Fujino, M., Kaneda, M., Miyazaki, T., Sugimoto, T. (2008). Relationship between catheter care and catheter-associated urinary tract infection at Japanese general hospitals: a prospective observational study. *International Journal of Nursing Studies, 45*(3), 352-361. doi:10.1016/j.ijnurstu.2006.10.006.

Tzeng, H. M. (2010). Inpatient falls in adult acute care settings: influence of patients' mental status. *Journal of Advanced Nursing,* doi:10.1111/j.1365-2648.2010.05343.x.

US Department of Health and Human Services. (1981). *National Nosocomial Infection Surveillance System Manual*. Atlanta, Georgia: Centers for Disease Control and Prevention.

Van Gennip, M., Christensen, L. D., Alhede, M., Phipps, R., Jensen, P. O., Christophersen, L., Bjarnsholt, T. (2009). Inactivation of the rhlA gene in Pseudomonas aeruginosa prevents rhamnolipid production, disabling the protection against polymorphonuclear leukocytes. *APMIS: Acta Pathologica, Microbiologica, Et Immunologica Scandinavica, 117*(7), 537-546. doi:10.1111/j.1600-0463.2009.02466.x.

Van Rompaey, B., Elseviers, M. M., Schuurmans, M. J., Shortridge-Baggett, L. M., Truijen, S., & Bossaert, L. (2009). Risk factors for delirium in intensive care patients: a prospective cohort study. *Critical Care (London, England), 13*(3), R77. doi:10.1186/cc7892.

Vesely, R. (2007). Insurers look to CMS' lead. Major players likely to follow rule on preventable errors. *Modern Healthcare, 37*(35), 20.

Voyer, P., Richard, S., Doucet, L., & Carmichael, P. H. (2009). Predisposing factors associated with delirium among demented long-term care residents. *Clinical Nursing Research, 18*(2), 153-171. doi:10.1177/1054773809333434.

Wagenlehner, F. M., Naber, K. G., & Weidner, W. (2005). Asymptomatic bacteriuria in elderly patients: significance and implications for treatment. *Drugs & Aging, 22*(10), 801-807.

Warren, J. W. (2001). Catheter-associated urinary tract infections. *International Journal of Antimicrobial Agents, 17*(4), 299-303.

Wei, L. A., Fearing, M. A., Sternberg, E. J., & Inouye, S. K. (2008). The Confusion Assessment Method: a systematic review of current usage. *Journal of the American Geriatrics Society, 56*(5), 823-830. doi:10.1111/j.1532-5415.2008.01674.x

Weng, T. I., Wu, H. Y., Lin, P. Y., & Liu, S. H. (2009). Uropathogenic Escherichia coli-induced inflammation alters mouse urinary bladder contraction via an interleukin-6-activated inducible nitric oxide synthase-related pathway. *Infection and Immunity, 77*(8), 3312-3319. doi:10.1128/IAI.00013-09.

Wilde, M. H., & Carrigan, M. J. (2003). A chart audit of factors related to urine flow and urinary tract infection. *Journal of Advanced Nursing, 43*(3), 254-262.

Wilson, M. L., & Gaido, L. (2004). Laboratory diagnosis of urinary tract infections in adult patients. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 38*(8), 1150-1158. doi:10.1086/383029.

Wiwanitkit, V., Udomsantisuk, N., & Boonchalermvichian, C. (2005). Diagnostic value and cost utility analysis for urine Gram stain and urine microscopic examination as screening tests for urinary tract infection. *Urological Research, 33*(3), 220-222. doi:10.1007/s00240-004-0457-z.

Woodford, H. J., & George, J. (2009). Diagnosis and management of urinary tract infection in hospitalized older people. *Journal of the American Geriatrics Society, 57*(1), 107-114. doi:10.1111/j.1532-5415.2008.02073.x.

Wullt, B. (2003). The role of P fimbriae for Escherichia coli establishment and mucosal inflammation in the human urinary tract. *International Journal of Antimicrobial Agents, 21*(6), 605-621.

Wullt, B., Bergsten, G., Connell, H., Rollano, P., Gebratsedik, N., Hang, L., & Svanborg, C. (2001). P-fimbriae trigger mucosal responses to Escherichia coli in the human urinary tract. *Cellular Microbiology, 3*(4), 255-264.

Yonkman, C. A. (1982). Cool and heated aerosol and the measurement of oral temperature. *Nursing Research, 31*(6), 354-357.

Yoshimura, N., & Chancellor, M. B. (2007). Physiology and pharmacology of the bladder and urethra. In A. J. Wein (Ed.), *Campbell-Walsh Urology* (9th ed.). Philadelphia: Saunders Elsevier.

Zarbock, A., & Ley, K. (2009). Neutrophil adhesion and activation under flow. *Microcirculation (New York, N.Y.: 1994), 16*(1), 31-42. doi:10.1080/10739680802350104.

Zasloff, M. (2007). Antimicrobial Peptides, Innate Immunity, and the Normally Sterile Urinary Tract. *Journal of the American Society of Nephrology, 18*(11), 2810-2816. doi:10.1681/ASN.2007050611.

Zdziarski, J., Svanborg, C., Wullt, B., Hacker, J., & Dobrindt, U. (2008). Molecular basis of commensalism in the urinary tract: low virulence or virulence attenuation? *Infection and Immunity, 76*(2), 695-703. doi:10.1128/IAI.01215-07.

Zou, Y., Cole, M. G., Primeau, F. J., McCusker, J., Bellavance, F., & Laplante, J. (1998). Detection and diagnosis of delirium in the elderly: psychiatrist diagnosis, confusion assessment method, or consensus diagnosis? *International Psychogeriatrics / IPA, 10*(3), 303-308.

APPENDIX A

TABLES

Table A.1. Patient Care Areas Used for Study Recruitment

Site A Patient Care Areas	Sites B and C Patient Care Areas
MEDICAL-SURGICAL General Medicine Telemetry Oncology	*MEDICAL-SURGICAL* General Medicine Telemetry Oncology
STEPDOWN Neurology Neurosurgery Cardiothoracic Surgery Respiratory Specialty Care Unit	*STEPDOWN* Intermediate Care Unit
INTENSIVE CARE Medical Intensive Care Neurosurgical Intensive Care Cardiothoracic Intensive Care General Surgery Intensive Care Trauma Intensive Care	*INTENSIVE CARE* Medical-Surgical Intensive Care

Table A.2. Antimicrobial Medications

Drug Class	Drug Name	Route
Penicillins	ampicillin	Enteral; Parenteral
	ampicillin-sulbactam	Parenteral
	amoxicillin-clavulanic acid	Enteral
	piperacillin-tazobactam	Parenteral
Cephalosporins	cephalexin	Enteral
	cefaclor	Enteral
	cefadroxil	Enteral
	cefuroxime	Enteral
	cefixime	Enteral
	cefprozil	Enteral
	cefpodoxime	Enteral
	Any	Parenteral
Tetracyclines	tetracycline	Enteral
	doxycycline	Enteral
	minocycline	Enteral
Fluoroquinolones	ciprofloxacin	Enteral; Parenteral
	levofloxacin	Enteral; Parenteral
	norfloxacin	Enteral
Aminoglycosides	gentamycin	Parenteral
	tobramycin	Parenteral
	amikacin	Parenteral
Carbapenems/Monobactams	aztreonam	Parenteral
	ertapenem	Parenteral
	imipenem-cilastatin	Parenteral
	meropenem	Parenteral
Miscellaneous	trimethoprim-sulfamethoxazole	Enteral
	Nitrofurantoin	Enteral
	Azithromycin	Enteral
	Fosfomycin	Enteral
	Fluconazole	Enteral; Parenteral

Table A.3. Analgesic Medications

Drug Class	Drug Name	Route
Non-Opioid	acetaminophen	Enteral
	acetylsalicylic acid	Enteral
	celecoxib	Enteral
	ibuprofen	Parenteral
	ketorolac	Enteral
	ibuprofen	Enteral
	naproxen or naproxen sodium	Enteral
Opioid	butorphanol	Parenteral
	codeine	Enteral
	fentanyl	Transdermal; Parenteral
	hydrocodone	Enteral
	hydromorphone	Enteral; Parenteral
	meperidine	Enteral; Parenteral
	methadone	Enteral
	morphine	Enteral; Parenteral
	oxycodone	Enteral
	oxymorphone	Enteral
	propoxyphene	Enteral
	tramadol	Enteral
Combination	acetaminophen-codeine	Enteral
	acetaminophen-hydrocodone	Enteral
	acetaminophen-morphine	Enteral
	acetaminophen-oxycodone	Enteral
	acetaminophen-propoxyphene	Enteral
	acetaminophen-tramadol	Enteral

Table A.4. Antipyretic Medications

Drug Name	Route
acetaminophen	Enteral
acetylsalicylic acid	Enteral
celecoxib	Enteral
ibuprofen	Enteral
methyl-prednisolone	Parenteral
naproxen or naproxen sodium	Enteral
prednisone	Enteral

Table A.5. Comorbidities

Manifestation	Disease
SUPRAPUBIC TENDERNESS	Abdominal Aortic Aneurysm
	Crohn's Disease
	Ulcerative Colitis
	Diverticulitis
	Intestinal Obstruction
	Hernia
	Perforated Bowel
	Dysmenorrhea
	Endometriosis
	Menses
	Ovarian Cyst or Tumor
	Pelvic Inflammatory Disease
	Nephrolithiasis
	Rectal Hematoma
	Bladder Distention
FLANK TENDERNESS	Herniated Intervertebral Disk
	Spinal Stenosis
	Ankiylosing Spondylitis
	Metastatic Spinal Tumor
	Multiple Myeloma
	Mechanical Back Sprain
	Vertebral Body Fracture
	Diskitis
	Spinal Osteomyelitis
	Epidural Abscess
FEVER	Viral Infection
	Bacterial Infection
	Mycobacterial Infection
	Fungal Infection
	Parasitic Infection
	Lymphoma
	Leukemia
	Renal Carcinoma
	Hepatic Carcinoma
	Autoimmune Disorder
	Heat Stroke
	Malignant Hyperthermia
	Thyroid Storm

Table A.5. continued

FEVER, CONT.	Adrenal Insufficiency
	Pulmonary Embolism
	Myocardial Infarction
	Crohn's Disease
	Ulcerative Colitis
DELIRIUM	Hypoglycemia
	Hypoxia
	Sodium Imbalance
	Hypercalcemia
	Hypercapnia
	Uremia
	Hyperthyroidism
	Stroke
	Subdural Hematoma
	Subarachnoid Bleed
	Postictal State
	Concussion
	Meningitis
	Encephalitis
	Brain Tumor
	Lithium Intoxication
	Ethanol Use
	Steroids
	Anticholinergics
	Sympathomimetics
	Poisons
	Drugs of Abuse
	Sepsis
	Thiamine Deficiency
	Niacin Deficiency

Table A.6. Template for 2x2 Contingency Tables for Manifestation Validity Testing

		CAUTI (at least 10^5 cfu/mL)	
		Present	Absent
Manifestation	Present	A	B
	Absent	C	D
		CAUTI (at least 10^3 cfu/mL)	
		Present	Absent
Manifestation	Present	A	B
	Absent	C	D
		CAUTI (uropathogenic E. coli at least 10^5 cfu/mL))	
		Present	Absent
Manifestation	Present	A	B
	Absent	C	D

Table A.7. Results of Screening and Enrollment at Site A, By Patient Care Area

Patient Care Area	# Screened	# Eligible	# Enrolled	% Enrolled of Screened	% Enrolled of Eligible	# Completed	% of Enrolled Completed	% of Eligible Completed
Medical Cardiology	8	8	4	50	50	2	50	25
Cardio-thoracic Surgery	27	27	8	29.6	29.6	6	75	22
Hematology – Oncology	5	5	0	0	-	-	-	-
Surgical Oncology	3	3	0	0	-	-	-	-
Neuro-science	35	33	9	25.7	27	3	33	9.1
General Medicine	19	19	10	52.6	52.6	4	40	21
Medical ICU	66	64	14	21.2	21.9	8	57	12.5
Respiratory Care Unit	3	3	0	0	-	-	-	-
Surgical ICU	110	107	20	18.2	18.7	4	20	3.7
TOTAL	**276**	**269**	**65**	**23.6**	**24.2**	**27**	**41.5**	**9.8**

Table A.8. Reasons for Study Nonparticipation at Site A, By Patient Care Area

Patient Care Area	Nonparticipation Rates	
Medical Cardiology	Reason for Nonparticipation	N (%)
	Intubated or Sedated	0
	Planned Catheter Removal Within 48 Hours	1 (25)
	Planned Discharge Within 48 Hours	0
	Patient / Guardian Declined Participation	3 (75)
	Other	0
Cardiothoracic Surgery	Reason for Nonparticipation	N (%)
	Intubated or Sedated	0
	Planned Catheter Removal Within 48 Hours	2 (10)
	Planned Discharge Within 48 Hours	5 (26)
	Patient / Guardian Declined Participation	6 (32)
	Other	6 (32)
Hematology-Oncology	Reason for Nonparticipation	N (%)
	Intubated or Sedated	1 (20)
	Planned Catheter Removal Within 48 Hours	0
	Planned Discharge Within 48 Hours	1 (20)
	Patient / Guardian Declined Participation	1 (20)
	Other	2 (40)
Surgical Oncology	Reason for Nonparticipation	N (%)
	Intubated or Sedated	0
	Planned Catheter Removal Within 48 Hours	2 (67)
	Planned Discharge Within 48 Hours	1 (33)
	Patient / Guardian Declined Participation	0
	Other	0
Neuroscience	Reason for Nonparticipation	N (%)
	Intubated or Sedated	4 (17)
	Planned Catheter Removal Within 48 Hours	7 (29)
	Planned Discharge Within 48 Hours	2 (8)
	Patient / Guardian Declined Participation	7 (29)
	Other	4 (17)
General Medicine	Reason for Nonparticipation	N (%)
	Intubated or Sedated	0
	Planned Catheter Removal Within 48 Hours	3 (33)
	Planned Discharge Within 48 Hours	1 (11)
	Patient / Guardian Declined Participation	4 (44)
	Other	1 (11)
Medical ICU	Reason for Nonparticipation	N (%)
	Intubated or Sedated	28 (56)
	Planned Catheter Removal Within 48 Hours	1 (2)
	Planned Discharge Within 48 Hours	2 (4)
	Patient / Guardian Declined Participation	9 (18)
	Other	10 (20)

Table A.8. continued

Respiratory Care Unit	Reason for Nonparticipation	N (%)
	Intubated or Sedated	0
	Planned Catheter Removal Within 48 Hours	0
	Planned Discharge Within 48 Hours	0
	Patient / Guardian Declined Participation	1 (33)
	Other	2 (67)
Surgical ICU	Reason for Nonparticipation	N (%)
	Intubated or Sedated	47 (54)
	Planned Catheter Removal Within 48 Hours	5 (5)
	Planned Discharge Within 48 Hours	3 (3)
	Patient / Guardian Declined Participation	12 (14)
	Other	20 (23)
TOTAL	Reason for Nonparticipation	N (%)
	Intubated or Sedated	80 (40)
	Planned Catheter Removal Within 48 Hours	21 (10)
	Planned Discharge Within 48 Hours	13 (6)
	Patient / Guardian Declined Participation	43 (21)
	Other	45 (22)

Table A.9. Results of Screening and Enrollment at Sites B and C, By Patient Care Area

Patient Care Area	# Screened	# Enrolled	% Enrolled of Screened
Medical-Surgical	35	13	37.1
Intermediate Care Unit	17	10	58.8
Intensive Care Unit	28	7	25
TOTAL	**80**	**30**	**37.5**

Table A.10. Reasons for Study Nonparticipation at Sites B and C, By Patient Care Area

Patient Care Area	Nonparticipation Rates	
Medical Surgical	Reason for Nonparticipation	N (%)
	Confused, Unable to Locate Proxy	2 (9.1)
	Patient / Guardian Declined Participation	18 (81.8)
	Other	2 (9.1)
Intermediate Care Unit	Reason for Nonparticipation	N (%)
	Confused, Unable to Locate Proxy	2 (28.6)
	Patient / Guardian Declined Participation	1 (14.3)
	Other	4 (57.1)
Intensive Care Unit	Reason for Nonparticipation	N (%)
	Confused, Unable to Locate Proxy	12 (57.1)
	Patient / Guardian Declined Participation	8 (38.1)
	Other	1 (4.8)
TOTAL	Reason for Nonparticipation	N (%)
	Confused, Unable to Locate Proxy	16 (32)
	Patient / Guardian Declined Participation	27 (54)
	Other	7 (14)

Table A.11. Participant Characteristics at Site A

Characteristic	**Number (%)** Participants	**Number (%)** Non-Participants
Sex		
Female	12 (44.4)	115 (46)
Male	15 (55.6)	134 (54)
Race		
White	26 (96.3)	230 (92.4)
Black or African-American	1 (3.7)	13 (5.2)
Native Hawaiian or Pacific Islander	0 (0)	0 (0)
American Indian or Alaskan Native	0 (0)	0 (0)
Asian	0 (0)	3 (1.2)
More Than One Race	0 (0)	0 (0)
Unknown or Not Reported	0 (0)	3 (1.2)
Ethnicity		
Hispanic	1 (3.7)	8 (3.2)
Non-Hispanic	26 (96.3)	234 (94)
Unknown or Not Reported	0 (0)	7 (2.8)
Mean Age (SD)	63.8 (14.8)	58 (16.3)
Mean Duration of Catheter Use Prior to Enrollment (SD)	14.4 (6.4)	13.3 (5.8)

Table A.12. Clinical Manifestations at Site A

Clinical Manifestation	**Frequency *(%)***
Fever	1 (3.7%)
Suprapubic Tenderness	5 (19%)
Flank Tenderness	1 (5%)
Delirium	2 (7.4%)

Table A.13. Type and Frequency of Microorganisms Isolated from Urine

Microorganism	**Concentration**	**Frequency *(%)***
Candida glabrata	$>10^5$	1 (3.7%)
Escherichia coli	$>10^3$	1 (3.7%)

Table A.14. Participant Characteristics at Sites B and C

Characteristic	**Number *(%)*** Participants	**Number *(%)*** Non-Participants
Sex		
Female	15 (50)	29 (58)
Male	15 (50)	21 (42)
Race		
White	22 (73.3)	36 (72)
Black or African-American	8 (26.7)	14 (28)
Native Hawaiian or Pacific Islander	0 (0)	0 (0)
American Indian or Alaskan Native	0 (0)	0 (0)
Asian	0 (0)	0 (0)
More Than One Race	0 (0)	0 (0)
Unknown or Not Reported	0 (0)	0 (0)
Ethnicity		
Hispanic	0 (0)	0 (0)
Non-Hispanic	30 (100)	50 (100)
Unknown or Not Reported	0 (0)	0 (0)
Mean Age *(SD)*	74.3 (11.99)	71.6 (16.5)

Table A.15. Clinical Manifestations at Sites B and C

Clinical Manifestation	**Frequency *(%)***
Fever	5 (16.7%)
Suprapubic Tenderness	10 (33.3%)
Flank Tenderness	5 (16.7%)
Delirium	6 (20%)

Table A.16. Validity of Clinical Manifestations at Bacteriuria Concentration Greater Than or Equal to 105 cfu/mL (*N* = 27 unless otherwise stated)

Manifestation	TP	FP	TN	FN	SENS	SPEC	PPV	NPV
Fever	0	1	25	1	0.00	0.96	0.00	0.96
Suprapubic Tenderness	0	5	21	1	0.00	0.81	0.00	0.95
Flank Tenderness (*N = 20)*	0	1	18	1	0.00	0.95	0.00	0.95
Delirium	0	2	24	1	0.00	0.92	0.00	0.96
MEAN					**0.00**	**0.91**	**0.00**	**0.96**

Table A.17. Validity of Clinical Manifestations at Bacteriuria Concentration Greater Than or Equal to 103 cfu/mL (*N* = 27 unless otherwise indicated)

Manifestation	TP	FP	TN	FN	SENS	SPEC	PPV	NPV
Fever	0	2	23	2	0.00	0.92	0.00	0.92
Suprapubic Tenderness	0	5	20	2	0.00	0.80	0.00	0.91
Flank Tenderness (*N = 20)*	0	1	17	2	0.00	0.94	0.00	0.89
Delirium	0	2	23	2	0.00	0.92	0.00	0.92
MEAN					**0.00**	**0.90**	**0.00**	**0.91**

Table A.18. Validity of Clinical Manifestations to Detect Uropathogenic E. coli (Phylogenetic classes B2 or D) at Bacteriuiria Concentration >103 cfu/mL (*N* = 27 unless otherwise stated)

Manifestation	TP	FP	TN	FN	SENS	SPEC	PPV	NPV
Fever	0	2	25	0	0.00	1.00	0.00	1.00
Suprapubic Tenderness	0	5	22	0	0.00	1.00	0.00	1.00
Flank Tenderness (*N = 20)*	0	1	19	0	0.00	1.00	0.00	1.00
Delirium	0	2	25	0	0.00	1.00	0.00	1.00
MEAN					**0.00**	**1.00**	**0.00**	**1.00**

Table A.19. Inter-Rater Reliability of Three Nurse Raters of CAUTI Clinical Manifestations

Clinical Manifestation	**Generalized Kappa Coefficient** (95% Confidence Interval)
Fever	1.00 (0.793 – 1.207)
Suprapubic Tenderness	0.39 (0.185 – 0.598)
Flank Tenderness (*N* = 12)	0.29 (-0.036 – 0.617)
Delirium	0.58 (0.379 – 0.792)

Table A.20. Frequency of CAUTI Manifestations, By Age Group (%)

Manifestation	**Age 65 and Older** *N* = 13	**Age < 65 Years** *N* = 14
Fever	0	1 (7.1)
Suprapubic Tenderness	0	5 (35.7)
Flank Tenderness	0	1 (10%)
Delirium	1 (7.7%)	1 (7.1%)
Any Manifestation	1 (7.7%)	6 (42.9%)

Table A.21. Validity of Clinical Manifestations to Detect Significant Bacteriuria at Urinary Concentration > or Equal to 105 cfu/mL, By Age Group.

Manifestation	Age 65 and Older	Age < 65 Years
Fever	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.93 PPV 0 NPV 0.93
Suprapubic Tenderness	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.62 PPV 0 NPV 0.89
Flank Tenderness	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.89 PPV 0 NPV 0.89
Delirium	Sensitivity 0 Specificity 0.92 PPV 0 NPV 1	Sensitivity 0 Specificity 0.92 PPV 0 NPV 0.92
MEAN	Sensitivity 0 Specificity 0.98 PPV 0 NPV 1	Sensitivity 0 Specificity 0.84 PPV 0 NPV 0.91

Table A.22. Validity of Clinical Manifestations to Detect Significant Bacteriuria at Urinary Concentration > or Equal to 103 cfu/mL, By Age Group

Manifestation	Age 65 and Older	Age < 65 Years
Fever	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.92 PPV 0 NPV 0.85
Suprapubic Tenderness	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.58 PPV 0 NPV 0.78
Flank Tenderness	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.88 PPV 0 NPV 0.78
Delirium	Sensitivity 0 Specificity 0.92 PPV 0 NPV 1	Sensitivity 0 Specificity 0.92 PPV 0 NPV 0.85
MEAN	Sensitivity 0 Specificity 0.98 PPV 0 NPV 1	Sensitivity 0 Specificity 0.83 PPV 0 NPV 0.92

Table A.23. Validity of Clinical Manifestations to Detect Uropathogenic E. coli (Phylogenetic classes B2 or D) at Bacteriuiria Concentration >103 cfu/mL, By Age Group.

Manifestation	Age 65 and Older	Age < 65 Years
Fever	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.93 PPV 0 NPV 0.93
Suprapubic Tenderness	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.64 PPV 0 NPV 1
Flank Tenderness	Sensitivity 0 Specificity 1 PPV 0 NPV 1	Sensitivity 0 Specificity 0.9 PPV 0 NPV 1
Delirium	Sensitivity 0 Specificity 0.92 PPV 0 NPV 1	Sensitivity 0 Specificity 0.93 PPV 0 NPV 1
MEAN	Sensitivity 0 Specificity 0.98 PPV 0 NPV 1	Sensitivity 0 Specificity 0.84 PPV 0 NPV 0.91

APPENDIX B

FIGURES

Figure B.1. Clermonth Method Two-Step Decision Model

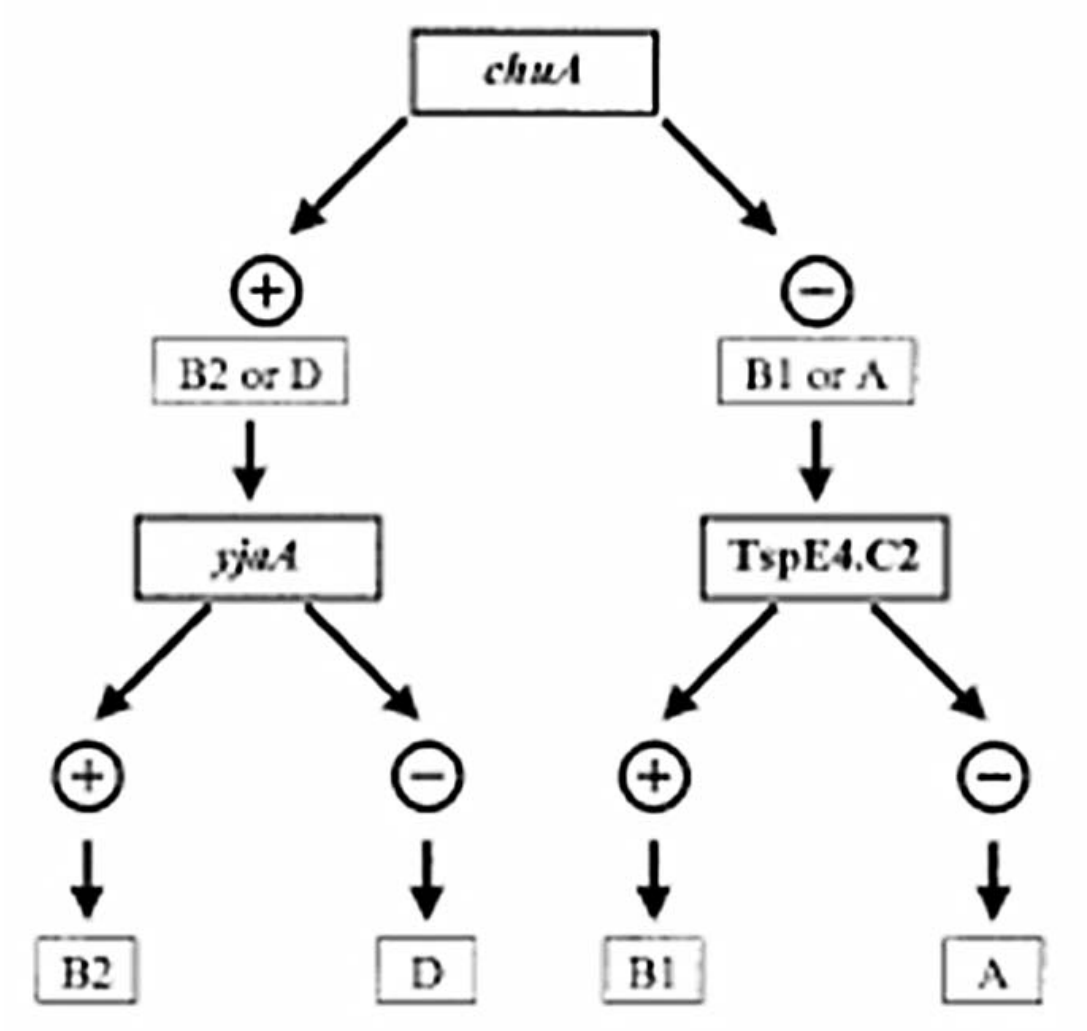


Figure B.2. Results of Screening and Enrollment at Site A

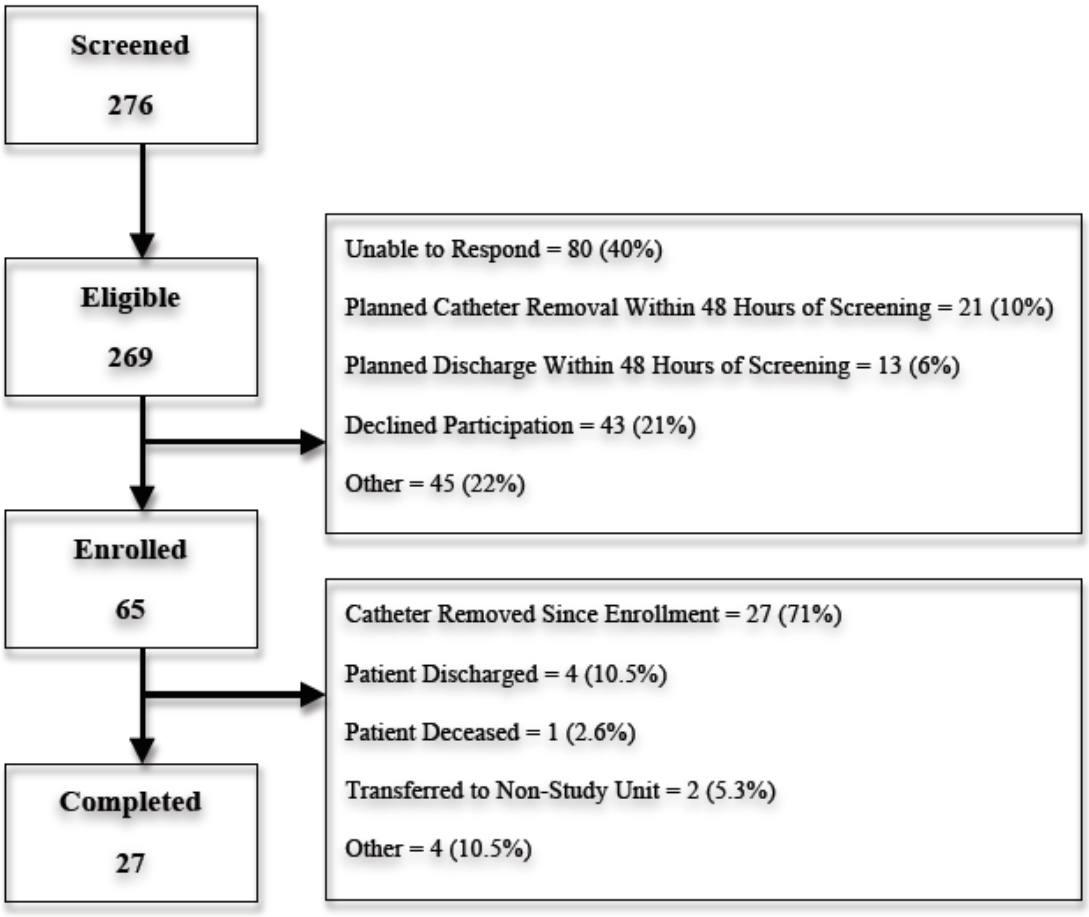
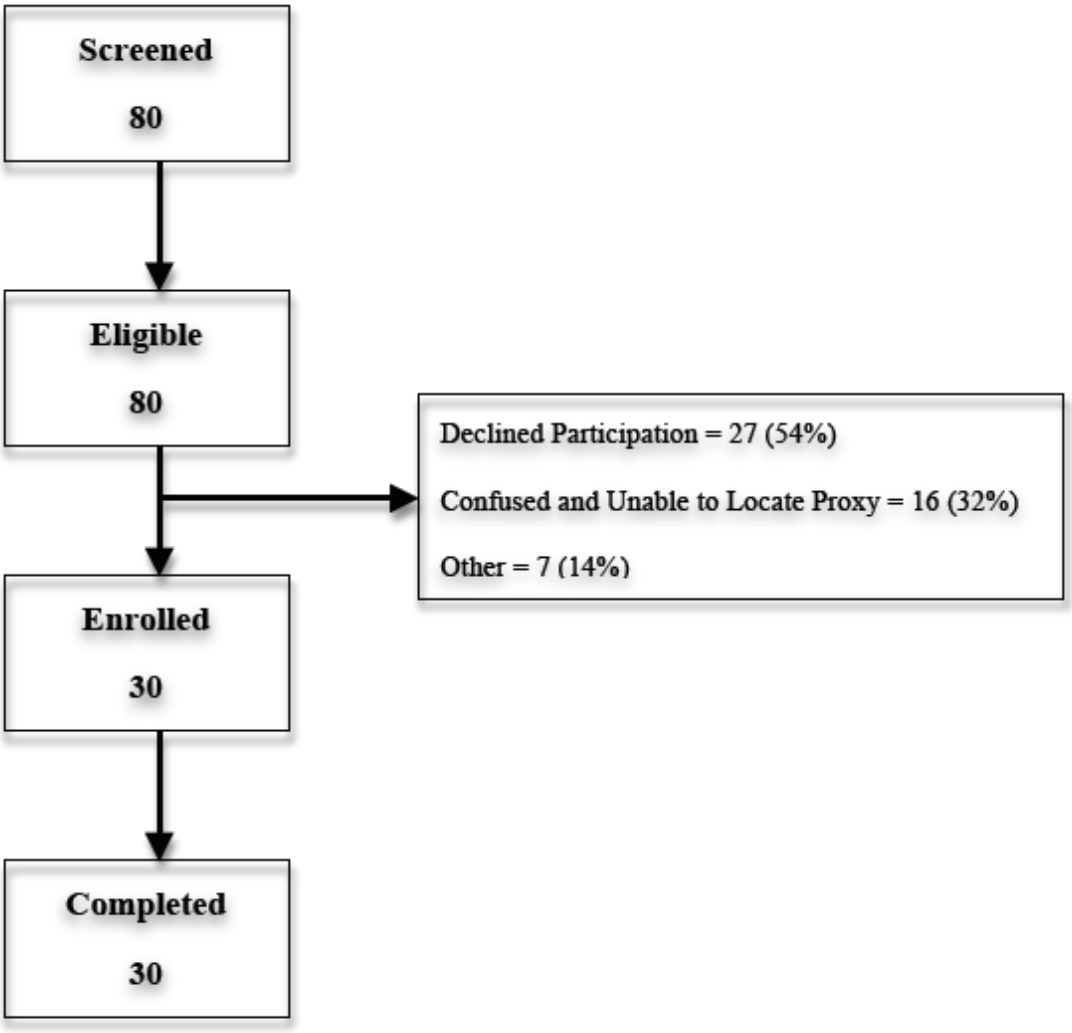


Figure B.3. Results of Screening and Enrollment at Sites B and C



APPENDIX C

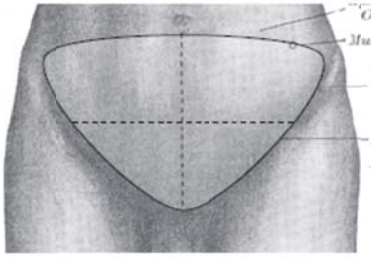
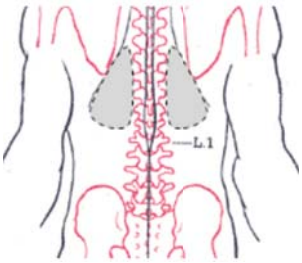
CAUTI ASSESSMENT OF MANIFESTATIONS PROFILE (CAMP) STUDY

Tom J. Blodgett, RN, PhD(c), Principal Investigator

CAUTI Assessment of Manifestations Profile (CAMP)

Subject ID: _____ **___ Rater 1**

Date of Visit: __ __ / __ __ / __ __ **___ Rater 2**

Parameter	*Result*	*Score*
Fever Use digital oral thermometer placed in the right sublingual pocket (may be used in those with ETT). *If temperature is greater than, or equal to, 38.0 ºC, fever is "Present"*	Present = 1 Absent = 0	
Suprapubic Tenderness 1. Palpate each abdominopelvic quadrant and the abdominopelvic midpoint using the anatomical landmarks provided below. 2. Press no deeper than 2 fingerbreadths. *If increased discomfort occurs during the palpation of any region, suprapubic tenderness is "Present"* 	Present = 1 Absent = 0	
Flank Tenderness 1. Assist subject to a sitting or side-lying position. 2. Percuss each costovertebral angle **once**, using the anatomical landmarks provided below. *If increased discomfort occurs during the percussion of either CVA, flank tenderness is "Present"* 	Present = 1 Absent = 0	
Delirium Feature / Considerations 1. Acute Onset or Fluctuating Course — Acute change in mental status from baseline? Did behavior fluctuate during the day? 2. Inattention — Difficulty focusing attention? 3. Disorganized Thinking — Incoherent, unclear, illogical, unpredictable? 4. Altered Level of Consciousness — Hyperalert, Lethargic, Stuporous, or Comatose? *Total Sub-Score* If features **1 and 2 and either 3 or 4** are present, delirium is "Present" (Inouye, van Dyck, Alessi, Balkin, Siegal, & Horwitz, 1990)	Present = 1 Absent = 0	

APPENDIX D

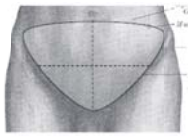
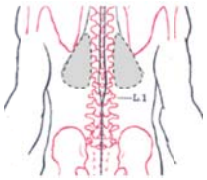
CAUTI ASSESSMENT OF MANIFESTATIONS PROFILE (CAMP) STUDY

Tom J. Blodgett, RN, PhD(c), Principal Investigator

CAUTI Assessment of Manifestations Profile – Sedated and Intubated (CAMP – SI)

Subject ID: _____ **___ Sedation Used at Time of Follow-Up Visit** **___ Rater 1**
___ Rater 2

Date of Visit: __ __ / __ __ / __ __ **___ Intubated at Time of Follow-Up Visit**

Parameter	Result	Score
Fever *If temperature is greater than, or equal to, 38.0 ºC, fever is "Present"*	Pres = 1 Abs = 0	
Suprapubic Tenderness  1. Palpate only once per quadrant and once at the midpoint, pressing no deeper than 2 fingerbreadths. 2. Observe for 3 indicators of pain with palpation: facial expression, UE movement, and MV compliance. 3. Match the patient's responses to palpation of each region to the findings described in the table. 4. As each region is palpated, write the number that corresponds to your findings in the "Score" column. *If any pain indicator score is **> 0** during the palpation of **any** region, suprapubic tenderness is "Present"*	Pres = 1 Abs = 0	
Flank Tenderness  1. Percuss only once per flank. 2. Observe for 3 indicators of pain with percussion: facial expression, UE movement, and MV compliance. 3. Match the patient's responses to percussion of each region to the findings described in the table. 4. As each region is percussed, write the number that corresponds to your findings in the "Score" column. *If any pain indicator score is **> 0** during the percussion of **either** region, flank tenderness is "Present"*	Pres = 1 Abs = 0	
Delirium (Inouye, van Dyck, Alessi, Balkin, Siegal, & Horwitz, 1990)	Pres = 1 Abs = 0	

Indicator	0	1	2	3	Score
Facial Expression	Relaxed	Partially Tightened	Fully Tightened	Grimacing	
Upper Limb Movement	No Movement	Partially Bent	Fully Bent with Finger Flexion	Permanently Retracted	
Compliance w/ Mechanical Ventilation	Tolerating Ventilation	Coughing, but Tolerating Ventilation	Fighting the Ventilator	Unable to Control Ventilation	
Total Sub-Score *If Total Sub-Score is greater than, or equal to, 1, this manifestation is "Present"*					

Indicator	0	1	2	3	Score
Facial Expression	Relaxed	Partially Tightened	Fully Tightened	Grimacing	
Upper Limb Movement	No Movement	Partially Bent	Fully Bent with Finger Flexion	Permanently Retracted	
Compliance w/ Mechanical Ventilation	Tolerating Ventilation	Coughing, but Tolerating Ventilation	Fighting the Ventilator	Unable to Control Ventilation	
Total Sub-Score *If Total Sub-Score is greater than, or equal to, 1, this manifestation is "Present"*					

Feature	Considerations
1. Acute Onset or Fluctuating Course	Acute change in mental status from baseline? Did behavior fluctuate during the day?
2. Inattention	Difficulty focusing attention?
3. Disorganized Thinking	Incoherent, unclear, illogical, unpredictable?
4. Altered Level of Consciousness	Hyperalert, Lethargic, Stuporous, or Comatose?
Total Sub-Score If features 1 and 2 and *either* 3 or 4 are present, delirium is "Present"	

APPENDIX E

CAUTI ASSESSMENT OF MANIFESTATIONS PROFILE (CAMP) STUDY

Tom J. Blodgett, RN, PhD(c), Principal Investigator

Screening Visit Protocol

1. Identify the time of urinary catheterization.
    a. Locate the patient's assigned staff RN.
    b. Identify yourself as a member of the CAMP Research Team from the University of Iowa College of Nursing.
    c. Verify that the staff RN is assigned to care for the potential subject.
    d. Ask them for their best estimate of the time the patient's urinary catheter was inserted.

2. Identify the age, sex, race, ethnicity, and location of the subject.
    a. Age and sex will be displayed in the Demographics tab.
    b. Race, ethnicity, and location data will be obtained from the patient's staff RN.

3. Identify the pregnancy status of the subject.
    a. Review the patient's History and Physical from the current hospital admission. This document can be found in the Chart Review Tab, under the current hospital encounter.

4. Examine the patient's urine for the presence of a baseline significant bacteriuria.
    a. Wash hands and apply non-sterile gloves.
    b. Cleanse the urine sampling port with an alcohol swab for three to five seconds. Ensure that the urine sample port does not come in contact with environmental surfaces (e.g. patient's skin). Allow alcohol to dry completely on sampling port.
    c. Attach the male end of a 3-mL luer-lock syringe to the urine sampling port.
    d. Aspirate 1 mL of urine into the syringe.
    e. Saturate the "nitrite" pad of the urinalysis test strip with the sample.
    f. Wait 2 minutes for test interpretation.
    g. Compare the nitrite pad of the urinalysis test strip to the interpretation key on the test strip bottle.
    h. Record the nitrite test result on the Screening Visit CRF.
        i. "Negative" – 0
        ii. "Positive" – 1+ or above
    i. Dispose of all used equipment in the trash.

APPENDIX F

CAUTI ASSESSMENT OF MANIFESTATIONS PROFILE (CAMP) STUDY

Tom J. Blodgett, RN, PhD(c), Principal Investigator

Screening Visit Case Report Form

MRN: ___ ___ - ___ ___ ___ ___ ___ - ___

Date of Screening: ___ ___ / ___ ___ / ___ ___

Time of Screening (24 hr clock): ___ ___ : ___ ___

Name:
First: _____ MI: __ Last: _____

Date of Birth: ___ ___ / ___ ___ / ___ ___

Sex:
_ M
_ F

Date of IUC Insertion: ___ ___ / ___ ___ / ___ ___

Time of IUC Insertion: ___ ___ : ___ ___

Age: ___ ___ years
(if < 18 years, exclude)

Catheter Duration: ___ ___ . ___ hours
(*if > 12 hours, exclude)*

Baseline UTI: ___ Yes ___ No
(if "yes," exclude)

Pregnant: ___ Yes ___ No
(if "yes," exclude)

ELIGIBLE? ___ Yes ___ No

If eligible, **ENROLLED?** ___ Yes ___ No

If not enrolled, why not?

___ Patient/guardian declined participation
___ Expected hospital discharge within 48 hrs
___ Expected catheter removal within 48 hrs
___ Other:
_____

SUBJECT ID: _____

Race:
___ American Indian or Alaskan Native
___ Asian
___ Native Hawaiian or Pacific Islander
___ Black or African-American
___ White
___ More than One Race
___ Unknown or Not Reported

Ethnicity:
___ Hispanic
___ Non-Hispanic
___ Unknown or Not Reported

Inpatient Unit:
___ Emergency Department
___ General Surgery
___ Orthopedic/Urologic Surgery
___ Cardiothoracic/Vascular Surgery
___ Neurosurgery
___ Gynecologic Surgery
___ Ear, Nose, Throat, Eye Surgery
___ Solid Tumor Surgery
___ Surgical ICU
___ Neurology
___ Burn/Trauma
___ Medical ICU
___ General Medicine A
___ General Medicine B
___ Medical Cardiology
___ Cardiovascular ICU
___ Hematology-Oncology
___ Adult BMT
___ Respiratory Specialty Care Unit

APPENDIX G

CAUTI ASSESSMENT OF MANIFESTATIONS PROFILE (CAMP) STUDY

Tom J. Blodgett, RN, PhD(c), Principal Investigator

Follow-Up Visit Protocol

1. Identify the hospitalization status of the patient *(Medical Record)*.
    a. Remains on screening unit
    b. Transferred to a study unit
    c. Transferred to a non-study unit
    d. Discharged or transferred out of study institution
    e. Deceased

2. Identify the catheterization status of the patient *(Direct Observation)*.
    a. Has remained catheterized since screening visit
    b. Catheter has been removed since screening visit

3. Identify the use of antimicrobial medications and document the drug class on the Follow-Up Visit CRF *(Medical Record)*.

4. Identify the use of analgesic medications and document the drug class on the Follow-Up Visit CRF *(Medical Record)*.

5. Identify the use of antipyretic medications and document their presence on the Follow-Up Visit CRF *(Medical Record)*.

6. Identify the presence of a confounding comorbidity and document the specific condition on the Follow-Up Visit CRF *(Medical Record)*.

7. Screen for the presence of cognitive impairment, using the Six-Item Screener.
    a. If cognitive impairment is present, use CAMP-CI

8. Screen for the presence of either the use of continuous sedation or endotracheal intubation.
    a. If subject is sedated or intubated, use CAMP-SI

9. Independently assess for the presence of clinical manifestations of CAUTI.
    a. While Rater 1 performs assessment, Rater 2 must wait outside subject's hospital room.
    b. Follow study procedures for assessment of each manifestation.

c. Each rater will document on separate copies of the appropriate version of the CAMP tool.
d. The CAMP score recorded by Rater 1 will be documented on the Follow-Up Visit Case Report Form.

10. Upon completion of the Rater 1 assessment, Rater 1 will obtain a urine specimen for microbiologic analysis, using the following procedure:
    a. Wash hands and apply non-sterile gloves
    b. Clamp urinary catheter tubing 6 inches distal to urine sampling port, using a rubberband or C-clamp, for 15-20 minutes. Tubing should remain clamped until the urine specimen is obtained.
    c. Cleanse urine sampling port with alcohol swab for 3-5 seconds. Ensure that urine sampling port does not come in contact with environmental surfaces (e.g. subject's skin, bed linens). Allow alcohol to dry on sampling port.
    d. Attach the male end of a 10-mL luer-lock syringe to the urine sampling port.
    e. Aspirate 10 mL of urine into the syringe.
    f. Unclamp the rubberband or C-clamp.
    g. Place a sterile "female end" luer-lock cap onto the "male end" of the luer-lock syringe. Complete the "CAMP Sample" label and affix it to the side of the syringe.
    h. Place the sample in a Biohazard bag for transport.
    i. Remove gloves.
    j. Wash hands.
    k. Deliver the specimens within 15 minutes, on ice, to the laboratory of Dr. Daniel Diekema.

11. Both raters will thank subject for their participation and inform them that their participation has ended.

12. Raters will debrief to ensure all steps have been performed.

APPENDIX H

CAUTI ASSESSMENT OF MANIFESTATIONS PROFILE (CAMP) STUDY

Tom J. Blodgett, RN, PhD(c), Principal Investigator

Follow-Up Visit Case Report Form

Subject ID: _____ **Date of Follow-Up:** ___ ___ / ___ ___ / ___ ___

Rater 1: _____ **Rater 2:** _____ **Time of Follow-Up** (24 hr clock): ___ ___ : ___ ___

Inpatient Unit at Follow-Up:

___ General Surgery
___ Urologic Surgery
___ Orthopedics
___ Cardiothoracic Surgery
___ Neurosurgery
___ Burn/Trauma
___ Gynecologic Surgery
___ ENT/Opthalmology
___ Surgical ICU
___ Neurology
___ Medical ICU
___ General Medicine
___ Adult BMT
___ Medical Cardiology
___ Cardiovascular ICU
___ Respiratory Care Unit
___ Medical-Surgical Oncology
___ Hematology-Oncology
___ ***SAME AS SCREENING VISIT***

Catheter Removed Since Screening?
___ No ___ Yes *(if yes, end participation)*

Patient Discharged or Deceased Since Screening?
___ No ___ Yes *(if yes, end participation)*

Patient On Non-Study Unit At Follow-Up?
___ No ___ Yes *(if yes, end participation)*

CAMP Version Used:

___ CAMP
___ CAMP-CI
___ CAMP-SI

Temperature: _____ ºC

CAMP Score: ____

Check all that apply:
___ None
___ Fever
___ Suprapubic Tenderness
___ Flank Tenderness
___ Delirium

Antimicrobial Medications:

___ None
___ Penicillins
___ Cephalosporins
___ Tetracyclines
___ Fluoroquinolones
___ Aminoglycosides
___ Carbapenems/MB's
___ Miscellaneous

Analgesic Medications:

___ Non-Opioid
___ Opioid
___ Combination

Antipyretic Medications

___ Present
___ Absent

Comorbidities:

___ AAA
___ Adrenal Insufficiency
___ Ankylosing Spondylitis
___ Anticholinergics
___ Autoimmune Disorder
___ Bacterial Infection
___ Bladder Distention
___ Brain Tumor
___ Concussion
___ Crohn's Disease
___ Diskitis
___ Diverticulitis
___ Drugs of Abuse
___ Dysmenorrhea
___ Encephalitis
___ Endometriosis
___ Epidural Abscess
___ Ethanol Use
___ Fungal Infection
___ Heat Stroke
___ Hepatic Carcinoma
___ Hernia
___ Herniated vertebral Disk
___ Hypercalcemia
___ Hypercapnia
___ Hyperthyroidism
___ Hypoglycemia
___ Hypoxia
___ Intestinal Obstruction
___ Leukemia
___ Lithium Intoxication
___ Lymphoma
___ Malignant Hyperthermia
___ Mechanical Back Sprain
___ Meningitis
___ Menses
___ Metastatic Spinal Tumor
___ Multiple Myeloma
___ Mycobacterial Infection
___ Myocardial Infarction
___ Nephrolithiasis
___ Niacin Deficiency
___ Ovarian Cyst or Tumor
___ Parasitic Infection
___ Perforated Bowel
___ Pelvic Inflammatory Dx
___ Poisons
___ Postictal State
___ Pulmonary Embolism
___ Rectal Hematoma
___ Renal Carcinoma
___ Sepsis
___ Sodium Imbalance
___ Spinal Osteomyelitis
___ Spinal Stenosis
___ Steroids
___ Stroke
___ Subarachnoid Hemorrhage
___ Subdural Hematoma
___ Sympathomimetics
___ Thiamine Deficiency
___ Thyroid Storm
___ Ulcerative Colitis
___ Uremia
___ Vertebral Body Fracture
___ Viral Infection

APPENDIX I

CAUTI ASSESSMENT OF MANIFESTATIONS PROFILE (CAMP) STUDY

Tom J. Blodgett, RN, PhD(c), Principal Investigator

Laboratory Results Case Report Form

Subject ID: _____

Date: ___ ___/___ ___/___ ___

QUANTITATIVE URINE CULTURE:

___ <10^3 cfu/mL

___ 10^3 cfu/mL or greater

Organism:

X = predominant organism
√ = also present at 10^3 or greater

___ *E. coli* (perform PCR)

___ *K. pneumoniae*

___ *P. aeruginosa*

___ *Enterococcus* spp.

___ *P. mirabilis*

___ *S. aureus*

___ Other *Staphyloccus* spp.

___ *C. albicans*

___ Other _____

POLYMERASE CHAIN REACTION:

chuA
___ Present ___ Absent

yjaA
___ Present ___ Absent

TspE4.C2
___ Present ___ Absent

FOR INVESTIGATOR USE ONLY:

***E. coli* Phylogenetic Class**

___ A (*chuA*- TspE4.C2-)

___ B1 (*chuA*- TspE4.C2+)

___ B2 (*chuA*+ *yjaA*+)

___ D (*chuA*+ *yjaA*-)