
Pathophysiology, Treatment, and Prevention of Catheter-Associated Urinary Tract Infection

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Urinary tract infections (UTIs) are among the most common microbial infections in humans and represent a substantial burden on the health care system. UTIs can be uncomplicated, as when affecting healthy individuals, or complicated, when affecting individuals with compromised urodynamics and/or host defenses, such as those with a urinary catheter. There are clear differences between uncomplicated UTI and catheter-associated UTI (CAUTI) in clinical manifestations, causative organisms, and pathophysiology. Therefore, uncomplicated UTI and CAUTI cannot be approached similarly, or the risk of complications and treatment failure may increase. It is imperative to understand the key aspects of each condition to develop successful treatment options and improve patient outcomes. Here, we will review the epidemiology, pathogen prevalence, differential mechanisms used by uropathogens, and treatment and prevention of uncomplicated UTI and CAUTI. **Key words:** CAUTI, prevalence, susceptibility, uncomplicated UTI, uropathogens

Urinary tract infections (UTIs), despite many efforts to manage them, still affect almost 11 million people in the United States¹ and almost 150 million worldwide² annually, placing UTIs among the most common microbial infections. UTIs cause serious sequelae, including frequent recurrences, pyelonephritis with sepsis, renal damage, and complications caused by constant or repetitive antimicrobial use, including multi-class antibiotic resistance and *Clostridium difficile* colitis.³ These consequences further emphasize the continued need to understand UTI pathophysiology and to develop new, efficient, and antibiotic-sparing therapies.

UTIs may be classified as uncomplicated or complicated.³ Uncomplicated UTIs, typically representing community-onset cystitis, are more frequent in outpatient settings⁴ and occur in otherwise healthy individuals without structural or neurologic abnormalities of the urinary tract. Uncomplicated UTIs occur predominantly in females of all ages but also in subsets of the male population (infant boys and older adult men).^{1,5} On the other hand, complicated UTIs are associated with patient-level factors that compromise urodynamics or host defenses, such as indwelling or intermittent urinary

catheterization, urinary obstruction (e.g., by stones) or retention, immunosuppression, renal failure, renal transplantation, and pregnancy.^{6,7} Indwelling urinary catheterization is the most common risk factor for complicated UTI; such catheter-associated UTI (CAUTI) accounts for 40% of all nosocomial infections worldwide^{5,8} and often leads to secondary bloodstream infections.^{5,9-11} Though recognition of this risk has led to reductions in insertion or duration of use of indwelling urinary catheters, a sizable number of hospitalized patients still undergo urinary catheterization during their stay. In the United States, the 30 million Foley catheters used annually confer substantial risk for CAUTI.¹²⁻¹⁶

As there are notable differences in clinical manifestations, causative organisms, and pathologic mechanisms between uncomplicated UTI and CAUTI, it is critical to dissect key aspects of each one to better assess specific treatment options and reduce the risks of complications and treatment failure. Here we will review and contrast the epidemiology, pathogen prevalence, differential mechanisms used by uropathogens, and treatment and prevention during uncomplicated UTI and CAUTI.

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Host Factors in Uncomplicated UTI and CAUTI

Uncomplicated UTI occurs significantly more often in women than in men^{1,3,17}; a nationwide US outpatient study showed that 84% of patients suffering UTI were women,¹⁸ and an earlier administrative data study of more than 10 million US emergency department UTI patients showed identically that 84% were female.¹⁹ These and other studies indicate that the female-to-male ratio in UTI is between 5:1 and 8:1.¹⁸⁻²⁰ It is estimated that 50% of women will experience at least one episode of UTI during their lifespan, and 25% of those women will experience recurrent UTIs (rUTIs).^{1,17} The majority of female UTIs manifest primarily in the lower urinary tract (community-onset cystitis); however, ascension of bacteria from the bladder can lead to kidney infection (pyelonephritis). Beyond female sex, other risk factors associated with cystitis include prior UTI, sexual activity, pregnancy, vaginal infection, diabetes, obesity, and genetic susceptibility.^{1,3,21}

The higher incidence of community-onset UTI in women is historically attributed to anatomic factors that enable transit of uropathogenic bacteria from a gastrointestinal tract reservoir to the urinary tract. Specifically, women have a shorter distance from anus to urethral opening and shorter urethral length than men and a vaginal/perineal microenvironment that may facilitate colonization of the urethra (and thus an indwelling catheter) by uropathogens. Among men, UTI incidence is higher in the elderly (where prostatic hypertrophy impairs urodynamics and promotes urinary retention) and in infants (where UTI incidence under 6 months of age is higher in boys than in girls).²²⁻²⁵ In comparison, gender disparity in CAUTI is comparatively narrow; epidemiologic studies show that 30% to 43% of CAUTI patients are male, yielding a female-to-male ratio of only about 2:1.^{3,26,27} Men who develop complicated UTI exhibit increased morbidity and mortality compared to women,²⁸⁻³¹ and morbidity from upper-tract UTI increases risk for hypertension and end-stage renal disease later in life.³²

Beyond anatomy, other sex differences that influence UTI susceptibility and severity are beginning to be identified, enabled by recent

advances in laboratory models of UTI. Historically, mouse modeling of UTI has been limited to females, as reliable access to the male mouse bladder via catheter insertion is technically challenging. Studies using a mini-surgical bladder inoculation method in both male and female mice show that once anatomic protections were bypassed in this way, male mice suffered more severe UTI, with strikingly higher incidences of chronic cystitis, severe pyelonephritis, and renal abscess formation.^{33,34} This increased morbidity of uropathogenic *Escherichia coli* (UPEC) UTI was shown to be driven by androgens: In C3H/HeN mice (a strain susceptible to cystitis and pyelonephritis), castrated males exhibited low bacterial loads and no abscess formation (equivalent to females), whereas treatment of castrated males with testosterone or 5 α -dihydrotestosterone (DHT; a non-hydrolyzable testosterone derivative) restored susceptibility to severe UTI phenotypes.^{33,35} In related studies, female C3H/HeN or C57BL/6 mice (a strain resistant to cystitis and pyelonephritis) treated with DHT exhibited higher bacterial loads and more frequent severe UTI outcomes (including abscesses) than placebo-treated females, whereas treatment of these androgenized females with enzalutamide, a second-generation androgen receptor antagonist, enabled them to clear UPEC effectively and avoid complications.³⁵ Though identification of androgens as drivers of a female-predominant disease may seem counterintuitive, epidemiologic data in specific, relevant populations do support a role for androgens in UTI susceptibility. First, infant males exhibit a postnatal burst of testosterone that returns to a prepubertal baseline by 6 months of age, matching the increased incidence of UTI in boys compared with girls in that interval.³⁶ Further, women with polycystic ovary syndrome, a common hyperandrogenic condition, may have an increased rate of UTI compared with their peers.^{37,38} Thus far, updated mouse models have identified altered cytokine responses as a possible mechanism underlying sex differences in UTI pathogenesis^{33,39}; however, other androgen-responsive mechanisms and pathways are actively being investigated.

In CAUTI, duration of catheterization is the most important determinant of bacteriuria,

and CAUTI risk increases by 3% to 7% each day after placement of an indwelling urinary catheter.⁴⁰ Even short-term urinary catheterization increases the risk of developing CAUTI and other complications up to 80%, and prolonged catheterization can increase the risk to nearly 100%.¹⁴⁻¹⁶ Furthermore, patients with catheter-associated bacteriuria have a 3% risk of developing bacteremia.⁴¹ Clinical studies have shown that the mechanical stress induced by urinary catheterization elicits histological and immunological changes in the bladder, resulting in a robust inflammatory response, exfoliation, edema, and mucosal lesions of the bladder epithelium and even affecting the kidneys.⁴²⁻⁴⁴ Furthermore, prolonged urinary catheterization results in ongoing epithelial irritation and persistent inflammation and has been linked with development of proliferative pathologies including squamous carcinoma, keratinizing squamous carcinoma, or cystitis granularis (which can progress to adenocarcinoma).⁴⁵ It is important to note that urinary catheterization not only induces ongoing inflammation but also interferes with normal micturition (voiding)¹ and mechanically impairs host defenses in the bladder, enabling microbial colonization, multiplication, and dissemination within the urinary tract.^{9,46,47} Additionally, inflammation elicited by the catheter can expose cryptic epithelial receptors that can be recognized and leveraged for colonization by the pathogen.⁴⁸ Recent studies in both mice and humans show that urinary catheterization-induced inflammation elicits fibrinogen release into the bladder to heal damaged tissue and prevent bleeding. Due to constant mechanical damage caused by the urinary catheter, fibrinogen accumulates in the bladder and deposits onto the catheter, at concentrations that increase with extended time of catheterization.⁴⁹⁻⁵¹ Some uropathogens, such as *E. faecalis*, *Staphylococcus aureus*, and *Candida albicans*, use fibrinogen to establish colonization (discussed below).⁴⁹⁻⁵³ Therefore, the presence of a urinary catheter and associated inflammation modify the bladder environment, offering a window of opportunity for microbial colonization and disease causation.

Pathogen Prevalence in Uncomplicated UTI and CAUTI

UPEC is the major causative agent of both uncomplicated UTI and CAUTI.⁵⁴⁻⁵⁶ In uncomplicated UTI, UPEC accounts for 75% to 85% of cases,^{3,54,55} followed by *Klebsiella pneumoniae* (~6%), *Staphylococcus saprophyticus* (~6%), and the remaining fraction comprising *Enterococcus* spp, group B streptococcus (GBS), *Proteus* spp, and *Pseudomonas aeruginosa*. In contrast, causative pathogens in CAUTI are more diverse than in uncomplicated UTI (**Figure 1**). A National Healthcare Safety Network (NHSN) review showed that UPEC accounts for just 23.9% of cases of CAUTI, followed by *Candida* spp (17.8%), *Enterococcus* spp (13.8%), *P. aeruginosa* (10.3%), *Klebsiella* spp (10.1%), *Proteus* spp (4%), *Enterobacter* spp (3.7%), coagulase-negative staphylococci (2.4%), *S. aureus* (1.6%), and even *Bacteroides* spp (<0.1%).⁵⁶ Notably, the catheterized bladder environment lowers the threshold for uropathogens that might not be successful otherwise and provides a platform for other opportunistic microbes to infect.

Virulence Mechanisms in Uncomplicated UTI

UPEC and *K. pneumoniae* are the most common uncomplicated UTI pathogens. Distinct from other uropathogens, UPEC and *K. pneumoniae* have dedicated mechanisms for (a) recognition, adherence, and invasion of urothelial cells; (b) replication inside the cell to form intracellular bacterial communities; and (c) bacterial dispersion and host cell re-invasion.^{1,13,17}

Recognition, Adherence, and Invasion of Urothelial Cells

After periurethral contamination by the gastrointestinal flora, UPEC cystitis isolate UTI89 and *K. pneumoniae* cystitis isolate TOP52 can colonize the urethra and ascend to the bladder; this migration may be enabled by the use of appendages such as flagella and pili.^{1,3,17} Once in the bladder lumen, UPEC and *K. pneumoniae* utilize the type

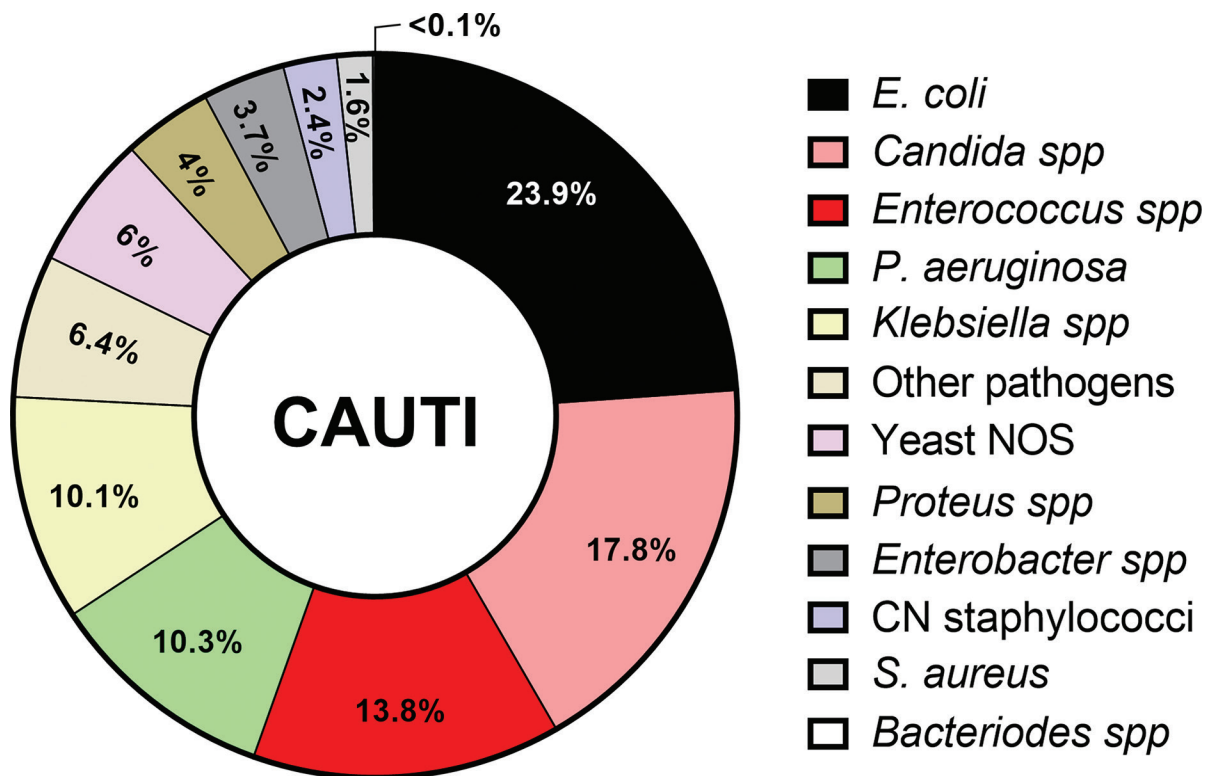


Figure 1. Catheter-associated urinary tract infection (CAUTI) uropathogen prevalence. CN = coagulase-negative; NOS = not otherwise specified.

1 pilus, specifically its tip adhesin FimH, to bind superficial umbrella cells of the uroepithelium.^{57,58} FimH recognizes mannose decorating the uroplakin protein UPIa, a major component of the apical surfaces of umbrella cells.⁵⁹ Expression of type 1 pili is critical for colonization, invasion, and establishment of cystitis.¹ In fact, *K. pneumoniae* (on the basis of encoding the “extra” type 1 pilus regulator *fimK*) appears programmed for reduced expression of type 1 pili, which may explain why it is a less prevalent agent of UTI than UPEC.⁵⁸ After adherence, some of the attached bacteria are internalized inside the umbrella cells with the purpose of replicating while subverting certain host defenses.^{57,60} The bacterial internalization cascade starts when Rho GTPases are activated, inducing actin rearrangement and internalizing surface-bound bacteria by plasma membrane engulfment.⁶¹ However, umbrella cells can also reverse this critical pathogenic step by expelling internalized UPEC. The expulsion mechanism relies on the recognition of Gram-negative lipopolysaccharide (LPS) by

Toll-like receptor 4 (TLR4) expressed on umbrella cells; this interaction leads to an increase in intracellular cyclic AMP, which prompts expulsion of UPEC-containing vesicles.^{3,62,63}

Replication Within Umbrella Cells Forming Intracellular Bacterial Communities

To evade expulsion, UPEC and *K. pneumoniae* escape the endocytic compartment and gain access to the umbrella cell cytoplasm by an undefined mechanism. The pathogen then rapidly multiplies forming type 1 pilus-dependent, biofilm-like intracellular bacterial communities (IBCs).⁶⁴ IBCs are initially loose collections of rod-shaped bacteria that subsequently mature into tightly packed, coccoid organisms.^{65,66} IBC formation is critical for acute cystitis, since bacteria in the IBC are inaccessible to the phagocytic action of arriving neutrophils.^{65,66} An important host response to bacterial invasion is to exfoliate IBC-containing umbrella cells, liberating IBCs into the urine.⁶⁷

Bacterial Dispersion and Host Cell Re-invasion

In a mature IBC, the bacteria in the periphery of the biofilm either adopt a filamentous phenotype or detach from the community; following bacterial fluxing from the umbrella cell, bacteria disperse with the purpose of invading naïve umbrella cells. This filamentous phenotype allows the bacteria to resist phagocytosis by neutrophils. To accomplish this phenotype, the bacterium requires the expression of the cell division inhibitor Sula, which enables elongation without septation.^{65,66,68} Once in the lumen of the bladder, the bacteria can either re-enter the IBC cycle or infect immature bladder cells exposed by exfoliation, consequently establishing quiescent intracellular reservoirs (QIRs). Distinct from IBCs, QIRs are composed of 4 to 10 nonreplicating bacteria that remain viable for months and are re-activated to seed recurrent UTIs. QIRs resist immune clearance and are not eradicated by antibiotic treatment.^{65,69,70}

Furthermore, survival in the urinary tract is essential for colonization, persistence, and dissemination. The bladder is an iron-limited environment; therefore, UPEC and *K. pneumoniae* utilize a variety of virulence factors to obtain nutrients, including several iron acquisition systems called siderophores.^{1,3,71,72}

Virulence Mechanisms in CAUTI

UPEC and *K. pneumoniae* cause UTIs regardless of the presence of a urinary catheter, due to these specialized mechanisms for bladder cell colonization and invasion.^{57,58,61,64-67,69,73} This section will focus on other prevalent CAUTI pathogens such as *Enterococcus* spp, *S. aureus*, *Candida* spp, *P. aeruginosa*, and *P. mirabilis*. The importance of the catheter in enabling pathogenesis by these organisms is exemplified by *E. faecalis* oral isolate OG1RF (model organism for CAUTI) and *S. aureus* isolate MRSA-1369, which are cleared from mouse bladders within a few days in the absence of a catheter but are able to establish persistent colonization during CAUTI.^{53,74} In the following sections, we will discuss the strategies that each pathogen uses to successfully cause CAUTI.

Enterococci

Enterococci have become the second most common bacteria recovered in CAUTI.^{3,9,40} *E. faecalis* uses endocarditis- and biofilm-associated (Ebp) pili for catheter adherence, colonization, and persistence during CAUTI.^{52,75-78} Initial *in vitro* characterization of *E. faecalis* OG1RF growth and biofilm in urine showed that *E. faecalis* was neither able to grow nor bind to the catheter material under these conditions.⁴⁹ This contradiction was explained by the finding that urinary catheterization-induced inflammation response results in the release of the host protein fibrinogen, which accumulates in the bladder and on the catheter. Fibrinogen is normally found in the bloodstream, is a marker of vascular rupture, and is responsible for coagulation, fibrosis, protection from infections, and other functions.⁷⁹ In CAUTI, the released fibrinogen is used by *E. faecalis* as a nutrient and a scaffold to form biofilms in the urinary catheter.⁴⁹ During growth in urine, *E. faecalis* induces the expression of two major secreted proteases, SprE and GeE, which degrade fibrinogen for nutrient acquisition. Host proteases also enable enterococci to utilize fibrinogen and play a major role in promoting inflammation and dissemination.⁸⁰ Furthermore, *E. faecalis* uses additional virulence factors to exploit fibrinogen-coated catheters and form biofilms during mouse and human CAUTI.^{49,50} *E. faecalis* expresses the Ebp pilus, tipped by the adhesin EbpA, which binds directly to fibrinogen via its N-terminal domain (EbpA^{NTPD}); this interaction is critical for the formation of catheter-associated biofilms and persistence.^{49,50}

Acquisition of nutrients, such as manganese (Mn), is essential for *E. faecalis* survival in the catheterized bladder. Mn is an essential micronutrient for bacterial pathogens during infection. In fact, one of the host mechanisms of defense is to reduce Mn availability to invading bacteria. To overcome this limitation, *E. faecalis* OG1RF contains three Mn transporters: one ABC-type (EfaCBA) and two Nramp-type transporters (MntH1 and MntH2). Deletion of all three Mn transporters from *E. faecalis* limits its ability to grow in Mn-minimal media or urine, and this

mutant is defective in causing CAUTI. Single and double deletions showed that MntH2 is the primary player in Mn acquisition during CAUTI.⁸¹

Staphylococcus aureus

Despite the fact that *S. aureus* accounts for only approximately 1.5% of all CAUTI,⁵⁶ *S. aureus* CAUTIs are frequently associated with severe sequelae, leading to increased rates of morbidity and mortality.⁵³ Like *E. faecalis*, methicillin-resistant *S. aureus* (MRSA) takes advantage of urinary catheterization-induced inflammation, using the released fibrinogen to facilitate catheter colonization during mouse and human CAUTI.⁷⁴ *S. aureus* strains are equipped with at least 20 fibrinogen-binding proteins.⁸² Interactions between MRSA and host fibrinogen are known to contribute to pathogenesis in other models of disease, such as central line infections and endocarditis.⁸³⁻⁸⁵ During CAUTI, *S. aureus* binds to fibrinogen via clumping factor B (ClfB).⁵³ However, distinct from *E. faecalis*, MRSA-1369 and other *S. aureus* strains are able to grow in urine conditions without the need to use fibrinogen as a protein source.⁵³

Proteus mirabilis

P. mirabilis forms biofilms on catheters⁸⁶ and accounts for 5% of CAUTI.⁵⁶ *P. mirabilis* is more prevalent in long-term catheterization patients and has become a common pathogen in nursing home residents.⁸⁷ *P. mirabilis* urinary isolate H14320 uses an arsenal of virulence factors including mannose-resistant *Proteus*-like (MR/P) fimbria, ureases, flagella, a variety of toxins and proteases, numerous secretion systems (types I, III, IV, V, and VI), and iron transporters.^{86,88} *P. mirabilis* uses MR/P fimbria to attach to urothelial cells or the catheter, facilitating biofilm formation.⁸⁹⁻⁹² During cystitis, *P. mirabilis* forms large communities on the luminal surfaces of bladder cells, in contrast to the IBC mechanism employed by UPEC and *K. pneumoniae*.^{64,69,86} During CAUTI, *P. mirabilis* produces ureases that hydrolyze urea to carbon dioxide and ammonia. The resulting increase in urinary pH induces precipitation of calcium crystals and magnesium ammonium phosphate, which then are incorporated into *P. mirabilis*

polysaccharide capsules, creating crystalline biofilms on the catheter. Crystalline biofilms provide protection for *P. mirabilis* against immune components, particularly neutrophils.⁸⁶ In the health care setting, 50% of patients with long-term catheterization (>28 days) experience catheter blockage by crystalline deposits,⁸⁶ which affects urine flow and may promote reflux of infected urine to the kidneys. Moreover, *P. mirabilis* flagella contribute to ascending UTI and confer motility on hard surfaces such as a urinary catheter.⁹³ To survive and grow in the urinary tract, *P. mirabilis* uses a variety of factors to obtain nutrients such as cytotoxin (hemolysin), proteases (ZapA and Pta), and iron acquisition systems (proteobactin, Nrp, and α -keto acids).⁸⁶

Pseudomonas aeruginosa

P. aeruginosa is responsible for about 10% of CAUTI,⁸¹ using a variety of factors to exploit the catheterized bladder. Biofilm formation of *P. aeruginosa* isolate PA01 (also a CAUTI model organism) is enabled by production of extracellular DNA (eDNA), rhamnolipids, lectins, elastases, and toxins.⁹⁴ Quorum sensing and exopolysaccharides are important for *P. aeruginosa* biofilm development in other environments but are not required for biofilm formation during CAUTI.^{95,96} Furthermore, bis-(3'-5') cyclic dimeric GMP (c-di-GMP) concentration levels influence *P. aeruginosa*-mediated biofilms during CAUTI.⁹⁷ Initially, *P. aeruginosa* promotes microcolony formation by using rhamnolipids, which modify the hydrophobicity of the bacterial cell surface. In later biofilm stages, rhamnolipids are responsible for migration initiation, enabling *P. aeruginosa* ascension in the urinary tract.^{94,98} *P. aeruginosa* expresses two siderophores, pyoverdinin and pyochelin, that are dedicated to scavenging iron. Additionally, *P. aeruginosa* produces elastases, exoenzyme S, and hemolytic phospholipase C that destroy host cells, releasing nutrients.^{99,100}

Candida spp

Candida is increasing as a causative agent of CAUTI, accounting for 17.8% of cases⁵⁶; however, its pathogenic mechanisms during CAUTI are not

well described.^{3,56,101} *Candida* species have been found associated with latex and silicone urinary catheters, with preference for latex material.¹⁰¹ *Candida* biofilms are readily detected on indwelling catheters by scanning electron microscopy.¹⁰² *C. albicans* adheres poorly to the bladder mucosa, and risk for *Candida* UTI increases sharply in the presence of an indwelling catheter.^{103,104} A recent ex vivo study showed that a *C. albicans* CAUTI isolate binds to urinary catheters via fibrinogen.⁵⁰ *C. albicans* encodes a fibrinogen-binding protein, Mp58, which is expressed during candidiasis.^{105,106} In total, the wide distribution of diverse fibrinogen-binding adhesins among common uropathogens suggests that fibrinogen binding is a common theme in CAUTI pathogenesis.⁵⁰

Prevention and Treatment of CAUTI

Urinary catheters are the most commonly used devices in hospitals; it is estimated that up to 25% of hospitalized patients undergo catheterization for different reasons such as urinary retention, surgical procedures, and prolonged immobilization.^{9,107,108} As our population ages, the use of urinary catheters becomes more frequent due to increased incidence of chronic and lifestyle-related diseases. Up to 13% of men and 12% of women have an indwelling urinary catheter on admission to nursing homes.¹⁰⁹ Hospitalizations resulting from catheter-related complications are increasing.¹¹⁰ In 2008, the Centers for Medicare and Medicaid Services ceased reimbursement for the increased costs of care resulting from hospital-acquired CAUTI.¹¹¹ In response, hospitals have developed strategies to reduce costs incurred and improve patient outcomes.¹¹²

Reducing Usage of Urinary Catheters and Minimizing Dwell Time

The Centers for Disease Control and Prevention (CDC) recommends minimizing urinary catheter use and duration, particularly in those at higher risk for CAUTI or mortality from catheterization such as women, the elderly, and patients with impaired immunity. CDC recommendations include the following: (a) avoid urinary catheterization to manage incontinence in patients and nursing

home residents; (b) use urinary catheters in operative patients only as necessary, rather than routinely; and (c) in operative patients who have an indication for an indwelling catheter, remove the catheter as soon as possible postoperatively, preferably within 24 hours.¹⁰⁸ Furthermore, recent bundles of interventions in clinical settings have shown success in reducing the incidence of CAUTI.¹¹³⁻¹¹⁵ These bundles focus on strategies to (a) reduce unnecessary placement of indwelling urinary catheters and encourage prompt removal and (b) ensure proper adherence to general infection control principles such as hand hygiene, surveillance/feedback of catheter use, aseptic insertions, proper maintenance, and education of clinical personnel.¹¹⁵ These interventions appear to be low cost, low risk, effective, and sustainable.¹¹⁵

Prophylactic Antibiotic Treatments

Control of CAUTIs has become a major challenge due to the development and dissemination of antibiotic resistance among the bacteria that cause health care–associated infections (HAI).^{9,116-118} Prophylactic antibiotics have been shown to promote the development of resistant organisms.⁸ Therefore, antibiotic stewardship initiatives have been developed to reduce the unnecessary use of antibiotics to curb development of resistant pathogens.¹¹⁹ Current CDC guidelines on management of CAUTI do not recommend the use of routine prophylaxis with systemic antibiotics for prevention of CAUTI in patients requiring short- or long-term urinary catheterization, unless clinical indications exist (e.g., in patients with bacteriuria upon catheter removal post urologic surgery).¹⁰⁸ Additionally, there is no recommendation for use of antimicrobial prophylaxis at the time of catheter removal.¹²⁰ Moreover, the CDC does not recommend the routine irrigation of the bladder with antimicrobial agents.¹⁰⁸ Therefore, best practice is to reduce unnecessary catheterization and minimize dwell time.

Antimicrobial-Coated Urinary Catheters

Microbial biofilm formation on the surface of the urinary catheters is the most common underlying cause of bacteriuria.¹²¹ Biofilm

formation is a microbial strategy to protect against antibiotic action and host immune defenses.¹²² Current CDC guidelines recommend the use of silicone catheters over other materials, because silicone catheters reduce the risk of encrustation in long-term catheterized patients who have frequent obstruction.¹⁰⁸ Therefore, efforts to prevent biofilm formation have been focused on developing antimicrobial/antiseptic-impregnated, silicone-based urinary catheters.^{123,124} Tested in vitro, these new catheters efficiently killed bacteria and prevented biofilm formation. However, in clinical settings they have proven unsuccessful in controlling CAUTI or have yielded mixed results.^{110,123,125,126} For example, a large multicenter randomized controlled trial of silver-alloy and nitrofurazone-releasing catheters showed no significant reduction in symptomatic CAUTI.¹²⁷

Treatment of CAUTI

Systemic antibiotic treatment is recommended for patients suffering CAUTI.^{110,128} A definite diagnosis of CAUTI requires bacteriuria between $\geq 10^3$ and $\leq 10^5$ CFU/mL with a positive urinalysis (defined by a positive dipstick, pyuria, or microorganisms seen on Gram stain).¹²⁹ After CAUTI is diagnosed, the catheter should be removed (if possible) or replaced by a new catheter before starting antimicrobial therapy. Empiric antibiotic therapy can be broad spectrum but later should be optimized according to culture and susceptibility results.¹¹⁰ Inappropriate management of CAUTI has been linked with development of bacteremia, which is more worrisome with multidrug-resistant uropathogens.¹³⁰ Therefore, appropriate management of CAUTI is important to reduce poor outcomes and mortality.^{110,130}

Future Therapies: Vaccine and Immunotherapies

Antibiotic treatment, the standard of care for CAUTI, is becoming increasingly challenging as multidrug resistance expands among uropathogens. In addition, antibiotic treatment exerts collateral effects such as intestinal dysbiosis that can create niches for colonization by multidrug-resistant

pathogens, which can ultimately dominate the gut microflora.¹³¹⁻¹³³ Thus, understanding the molecular basis of host-pathogen interactions in CAUTI is crucial for development of efficient antibiotic-sparing intervention strategies and for preventing the further evolution of multidrug-resistant uropathogens.

A vaccine strategy targeting enterococcal interactions with fibrinogen may hold considerable promise, since EbpA is highly conserved among the enterococci and is critical for catheter colonization. In a mouse model of CAUTI, active immunization with EbpA^{NTD} protected mice against infection.⁴⁹ Similarly, passive immunotherapy using anti-EbpA^{NTD} antibodies protected mice against *E. faecalis* CAUTI prophylactically and therapeutically. Notably, these antibodies disrupted established biofilms in vivo, which are well known to be difficult to eradicate in clinical settings. Furthermore, this immunotherapy was effective in treating CAUTI caused by a diverse collection of enterococcal clinical isolates from the urinary tract, bloodstream, and gastrointestinal tract, including representatives of *E. faecalis*, *E. faecium*, *E. gallinarum*, and vancomycin-resistant enterococci, as well as several unclassified enterococcal isolates.⁵¹ Thus, development of adhesin-based vaccines and monoclonal immunotherapies represent a promising avenue for novel therapeutics against selected uropathogens.

Outlook

Infection prevention and control represent a paramount achievement of modern medicine. Though urinary catheters are often necessary in managing complicated patients, these devices make patients susceptible to infections. CAUTIs impose a substantial threat to public health, and their treatment and control is becoming challenging due to the rise of antibiotic-resistant uropathogens. Recent discoveries of the adverse health effects of gut microbiota disruption provide additional impetus to reduce antibiotic use. Current research into understanding host-uropathogen interactions is moving the field toward new antibiotic-sparing approaches to CAUTI, with promising results.

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