Urinary Tract Infections: Current and Emerging Management Strategies

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Acute cystitis is one of the most commonly encountered bacterial infections and is responsible for substantial morbidity and high medical costs in the United States and across the globe. Though generally considered to be self-limiting and easily treated with antibiotics, urinary tract infections (UTIs) are often incompletely resolved by antibiotic therapy and frequently recur. This is in part due to the ability of uropathogenic bacteria to invade, replicate, and persist within host epithelial cells. The biological complexity of these infections combined with a dramatic rise in antibiotic-resistant pathogens highlight the need for alternative therapies. In this review we examine current management strategies for UTIs, as well as emerging treatments, including novel compounds that block bacterial interactions with the urothelium and vaccines focused on preventing both acute and recurrent infections.

Keywords. UPEC; antibiotic resistance; vaccine; cystitis; recurrent UTI.

A urinary tract infection (UTI) is defined as microbial infiltration of the otherwise sterile urinary tract and is one of the most common bacterial infections worldwide. UTIs encompass infections of the urethra (urethritis), bladder (cystitis), ureters (ureteritis), and kidney (pyelonephritis). There is an estimated annual occurrence of well over 8 million UTIs in the United States, many of which result in a visit to a physician [1]. Nearly all patients with UTI are prescribed a regimen of antibiotics, with roughly 1% of patients requiring hospitalization. The annual cost of UTI treatment in the United States is estimated at $2.14 billion [2], a value compounded by the frequency of recurrent infections. In this review we discuss the epidemiology of acute and recurrent UTIs, detail current management strategies, and explore emerging therapeutics.

EPIDEMIOLOGY OF UTIs

UTIs are the most frequent bacterial infection seen in the outpatient setting: 1 in 3 women will develop a UTI requiring antibiotic treatment by age 24, and 50% experience at least 1 UTI during their lifetime [1]. The incidence of cystitis is significantly higher in women than men, likely the result of anatomic differences. Specifically, the shorter female urethra can facilitate bacterial transit from the urethral opening to the bladder. Colonization of the vaginal introitus by gastrointestinal pathogens can also increase the likelihood of urinary tract infiltration [3, 4]. Other factors, including urinary tract obstruction, incomplete voiding, and aberrant structural anatomy also predispose individuals to UTIs. Additional risk factors include prior history of UTIs, vaginal intercourse within the past 2 weeks, use of contraception with spermicide, low vaginal estrogen levels [1, 5], and individual genetic background (extensively reviewed in [6]). While a number of comorbidities increase susceptibility to UTI, the majority of UTIs occur in otherwise healthy women.

The most common bacterial cause of uncomplicated community-acquired UTI is uropathogenic *Escherichia coli* (UPEC), representing >80% of infections [1]. These

bacteria inhabit the lower intestinal tract of warm-blooded vertebrates where they lead a seemingly innocuous existence until they gain access to a niche, such as the urinary tract, where they can cause disease. Other pathogens commonly associated with uncomplicated UTI include *Staphylococcus saprophyticus*, *Klebsiella* species, *Proteus mirabilis*, and *Enterococcus faecalis* [7].

One of the more ominous issues on the horizon for bacterial infections, with UTIs being no exception, is the rise of antibiotic-resistant organisms. One especially troubling example is the heightened incidence of sequence type 131 (ST131) strains of UPEC around the world. These strains often exhibit high levels of resistance to multiple antibiotics and have undergone rapid intercontinental dispersal over the last decade [8]. ST131 strains are an increasingly common cause of community-acquired UTIs, spurring efforts to better identify and treat these resilient pathogens [8, 9]. Factors driving the global spread of ST131 strains are incompletely understood, but likely include the acquisition of antibiotic resistance genes, such as those encoding extended-spectrum β-lactamases (ESBLs), and the capacity to effectively utilize a broad range of metabolites [8, 10]. These characteristics may give ST131 strains a competitive advantage within host environments, increasing the likelihood of their dissemination within and between individuals.

RECURRENT UTIs AND INTRACELLULAR BACTERIAL RESERVOIRS

The burden of UTIs is compounded by their high rate of recurrence. Recurrent UTI (rUTI)—defined as 2 uncomplicated infections in a 6-month time period or 3 infections within a year—cause a tremendous amount of morbidity and are frustrating to patients and physicians alike [1]. Despite administration of antibiotics that seemingly clear the infection (determined by negative urine cultures), the probability that a patient will develop a second UTI within 6 months is 25%, with the chance of recurrence over a 12-month period increasing to 46%. The historical view of rUTI pathogenesis is that each recurrence represents an independent inoculation of the urinary tract. However, this model does not satisfactorily explain many (>50%, by some estimates) rUTI episodes in which the bacterial strains responsible for both the initial infection and the recurrence are genetically identical [11]. An alternative mechanism for recurrence involves the establishment of protected, intracellular bacterial reservoirs within the bladder mucosa (Figure 1).

UPEC can invade host epithelial cells, including the terminally differentiated superficial umbrella cells that line the lumen of the bladder, as well as the underlying, immature
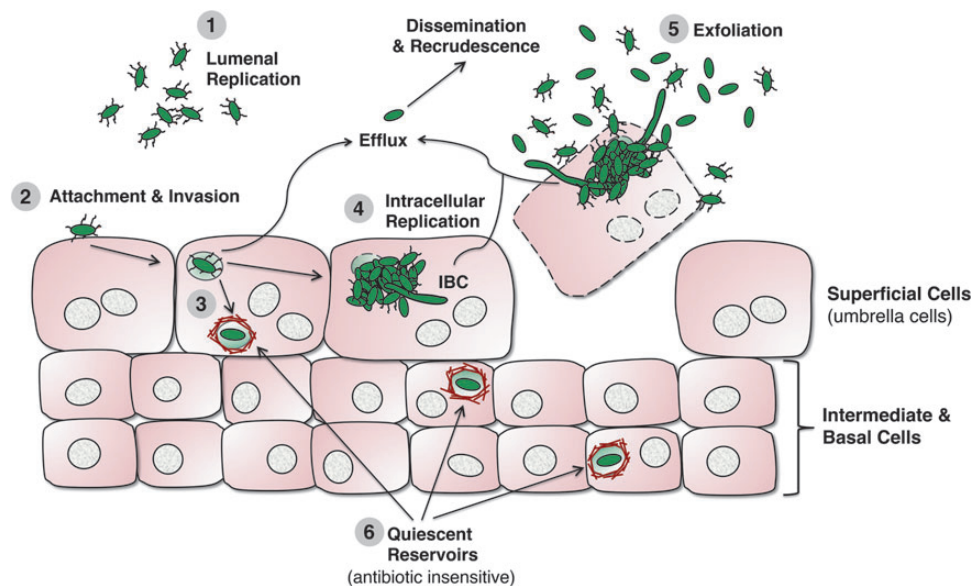
Figure 1. Events that promote the establishment and recurrence of urinary tract infection (UTI). (1) During a UTI, uropathogenic *Escherichia coli* (UPEC; green) can replicate within the lumen of the bladder or (2) attach to and invade bladder epithelial cells. (3) Following invasion, UPEC is either shuttled back out to the lumen or trafficked into late endosome-like compartments. (4) Disruption of these compartments and subsequent entry of UPEC into the host cytosol allows for rapid intracellular bacterial growth and the development of intracellular bacterial community. During these events, UPEC can acquire alternate morphologies, including the formation of long, filamentous cells that are resistant to host defenses such as neutrophils. (5) Infection can trigger the exfoliation of bladder cells, a process that aids in the elimination of adherent and internalized bacteria. The efflux of UPEC from host bladder cells, including those undergoing exfoliation, facilitates pathogen dissemination within and between hosts. (6) UPEC that remains bound within late endosome-like compartments in the urothelium can establish long-lived intracellular quiescent reservoirs that are often enmeshed within actin filaments (red) and extremely difficult to eradicate with antibiotic treatments. The resurgence of UPEC from these reservoirs can initiate recrudescent infections. Abbreviation: IBC, intracellular bacterial community.

intermediate and basal cells [12]. Within superficial bladder cells, UPEC can enter the host cytosol and rapidly multiply, forming a biofilm-like assembly known as an intracellular bacterial community (IBC) [12, 13]. The development of IBCs can enhance the ability of UPEC to establish itself within the urinary tract, building up large numbers of bacteria while sequestered away from the flow of urine and the influx of inflammatory cells and antibacterial molecules. IBCs, however, are not long-lived and will eventually disperse or be shed along with the infected host cells [14]. Indeed, the remnants of IBC-containing host cells can be detected in urine samples isolated from women seeking treatment for UTIs [3]. The efflux of UPEC from within IBCs, as well as the eventual exfoliation of the infected superficial cells, may potentiate the dissemination of UPEC both within the urinary tract and between hosts.

Rather than forming an IBC, UPEC can enter a dormant state within host epithelial cells after trafficking into membrane–bound compartments that become enmeshed within host actin filaments [12]. The quiescent nature and intracellular localization of these bacteria renders them resistant to most antibiotics and inaccessible to infiltrating neutrophils and other host defenses [13, 14]. Experimental models indicate that these quiescent intracellular UPEC reservoirs can persist for long periods in the absence of any overt clinical symptoms, even with the use of antibiotic treatments that effectively sterilize the urine [14]. Environmental signals, such as the reorganization of actin filaments that occurs as bladder cells undergo terminal differentiation, can trigger the resurgent growth of UPEC, prompting the development and dispersal of IBCs and the reinitiation of clinical symptoms. According to this model, rUTIs may in many instances be more accurately defined as recrudescent infections. These issues highlight the need for therapeutic strategies that effectively target both active and dormant stages of UTI.

CURRENT MANAGEMENT OF UTIs

Initial diagnosis of acute uncomplicated cystitis is typically based on patient medical history, taking into account past individual and family health issues, sexual activity, and current symptoms. Common indicators of acute cystitis include urinary urgency and frequency, pain when voiding (dysuria), lower abdominal discomfort, and cloudy or dark urine. The diagnosis of patients presenting with these classic symptoms may be confirmed by urinalysis showing the presence of red blood cells, high nitrite levels, and leukocyte esterase in the urine.

Although medical history and urinalysis are sufficient for the diagnosis of most uncomplicated UTIs, the gold standard for diagnosis of acute cystitis includes a bacteriological urine culture with identification of the causative agent and antimicrobial susceptibility testing. Using fresh, midstream urine, clinical confirmation of an uncomplicated UTI is classically defined as $\geq 10^5$ colony-forming units (CFU)/mL of urine. However, this definition has recently been modified based on observations that many uropathogens are capable of eliciting clinical pathology in the urinary tract even with low levels of bacteriuria [1]. Consequently, as little as 10^3 CFU/mL urine, in the presence of overt UTI symptoms, is now considered sufficient for diagnosis of acute cystitis [15]. Current recommended treatments for acute uncomplicated cystitis are described in Table 1 [1, 16].

Treatment of rUTI

For women who suffer from rUTI, low-dose antibiotic prophylaxis such as nitrofurantoin (100 mg per day), cephalexin (250 mg daily) or trimethoprim-sulfamethoxazole (40 mg/200 mg daily) can provide symptomatic relief and protection against subsequent infections [17]. For women whose UTIs are coincident with sexual activity, a single, postcoital prophylactic antibiotic can be effective in preventing infections [18]. Self-initiated antibiotics are also useful for women with frequent recurrent infections. After diagnosing themselves based on symptoms and/or a urine dipstick, they can initiate a 3-day regimen without needing to visit a physician [18].

The increasing prevalence of antibiotic-resistant uropathogens is likely to limit the effectiveness of our current antibiotic arsenal. For example, individuals who suffer from serious recurrent or chronic UTIs due to ESBL-producing ST131 strains may benefit greatly from carbapenems such as ertapenem [9], but these antibiotics are considered one of our last lines of defense and so should be used cautiously. The ongoing emergence of antibiotic-resistant strains, in conjunction with the high frequency of rUTIs, highlights the need for a better understanding of these infections and the development of new therapeutic strategies.

EMERGING THERAPIES

As noted above, many rUTIs are thought to arise from the ability of bacteria to attach to and invade the bladder mucosa, where they can form intracellular reservoirs protected from antibiotics and host defenses. As such, many emerging treatments for UTIs are aimed at blocking adhesion of bacteria to the urothelium and thereby preventing the establishment of troublesome reservoirs. Type 1 pili (or fimbriae), which are multiprotein filamentous adhesive structures encoded by virtually all UPEC isolates, are generally indispensable for colonization of the urinary tract [11]. The adhesin protein FimH, which is localized at the distal tip of each type 1 pilus, binds mannose residues on host glycoprotein receptors and allows UPEC to adhere to and invade host bladder cells [19]. Type 1 pili also promote biofilm formation and the development of IBCs [20]. Because type 1 pili are important colonization factors, the

Table 1. Common Treatment Options for Uncomplicated Cystitis

Antibiotic	Mechanism	Dosage	Notes
Nitrofurantoin monohydrate/macrocrystals	Inhibits protein, DNA, RNA, and cell wall synthesis	100 mg orally, twice daily for 5 d	Low resistance rates and risk of adverse side effects. Similar efficacy compared to a 3-d regimen of trimethoprim-sulfamethoxazole
Trimethoprim-sulfamethoxazole	Inhibits nucleic acid synthesis by folate synthesis inhibition	160 mg/800 mg (1 double-strength tablet), twice daily for 3 d	Only for use when local resistance rates do not exceed 20% and in patients who do not have sulfa drug allergies
Fosfomycin trometamol	Blocks cell wall synthesis by inactivating enolpyruvyl transferase	3 g in a single dose	Minimal resistance and risk of collateral damage. Inferior efficacy compared to other regimens
Pivmecillinam	Disrupts synthesis of cell wall by inhibiting formation of peptidoglycan cross-links	400 mg, once daily for 3–7 d	Low resistance rates and risk of adverse side effects. Not available in North America

The choice of antibiotics should be made after considering patient allergy and compliance history, local resistance rates, drug availability, and cost. Fluoroquinolones such as ciprofloxacin are highly effective and can be given if none of the recommended antimicrobials can be used. However, resistance rates to these drugs are on the rise and it is recommended that they be reserved for conditions other than acute cystitis. β-lactam antibiotics, such as amoxicillin, cefdinir, cefaclor, or cefpodoxime, in 3- to 7-day treatment regimens can be given when other recommended agents cannot be used. However, β-lactam antibiotics have inferior efficacy and a higher rate of resistance, particularly in ST131 strains. Ampicillin should not be used because it displays relatively poor efficacy in the treatment of urinary tract infections and resistance rates to ampicillin are typically high.

therapeutic potential of inhibiting the assembly or function of these adhesive organelles has received considerable attention.

Pilicides and Mannosides

The assembly of type 1 pili occurs through the chaperone-usher pathway, relying on the periplasmic chaperone FimC for the stabilization, folding, transport, and assembly of pilus subunits [21]. Small synthetic molecules known as pilicides, which are designed to target periplasmic chaperones and consequently interfere with pilus assembly, provide an attractive approach for blocking bacterial adhesion and subsequent reservoir formation. In vitro, pilicides effectively inhibit pilus biogenesis, reducing UPEC adherence to bladder epithelial cells as well as type 1 pili–dependent biofilm formation [22, 23]. The efficacy of pilicides in animal infection models has not been reported.

Researchers have also specifically targeted the FimH adhesin by use of soluble receptor analogues, or mannosides, that act as antiadhesives. These molecules bind FimH and prevent it from interacting with host receptors [24]. Recently, orally available mannoside derivatives have been developed that show great promise as therapeutics [25, 26]. In a murine UTI model, these agents work prophylactically, preventing bacterial invasion into bladder tissue [26]. They can also be used to treat established and catheter-associated infections, acting synergistically with standard antibiotic treatments to reduce UPEC titers within the urinary tract of infected mice [27].

Both mannosides and pilicides have exciting potential as future therapies for the treatment of uncomplicated cystitis and rUTI, and both types of reagents may help circumvent the rising tide of antibiotic-resistant organisms. However, one potential concern with the systemic administration of either mannosides or pilicides is potential adverse effects on commensal *E. coli* strains and other members of the intestinal microbiota, many of which also express type 1 pili [28]. Current thinking by many in the field is that use of pilicides and mannosides will likely be less disruptive than current antibiotic treatment protocols, but this supposition requires additional investigation.

Vaccinology

An alternate strategy for the prevention of recurrent and chronic UTIs is the development of systemic or mucosal vaccines. Over the past 20 years, several vaccination approaches have been explored, including the use of heat-killed whole bacteria, bacterial cell extracts, and purified UPEC-associated virulence factors as antigens. Vaccination of women using a vaginal suppository containing 10 heat-killed strains of uropathogenic bacteria showed much promise in recent years [29, 30]. This multivalent vaccine formulation, known as Solco Urovac, included 6 *E. coli* strains plus 1 strain each of *P. mirabilis*, *Morganella morganii*, *Klebsiella pneumoniae*, and *E. faecalis*. Urovac passed phase 2 clinical trials and was shown to reduce the incidence of UTI caused by *E. coli* in sexually active women

between 20 and 50 years of age with histories of rUTI [29]. Although some individual patients in the study showed increases in anti–*E. coli* antibody levels, no statistically significant differences between vaccinated and placebo control groups were detected, possibly accounting for the lack of any follow-up phase 3 trials.

Specific bacterial factors that have been targeted as vaccine candidates for UTI include the type 1 pilus–associated adhesin FimH and UPEC-associated iron acquisition systems. Like pilicides and mannosides, antibodies directed against FimH can interfere with the functionality of type 1 pili, disrupting the ability of UPEC to colonize the urinary tract. Vaccination with purified FimH coupled to its periplasmic chaperone FimC offered protection against UPEC when administered systemically in both murine and primate models of cystitis [31–33]. A similar vaccine containing a truncated version of FimH protected mice from experimentally induced cystitis when given by either intramuscular or intranasal (mucosal) inoculation, using CpG oligonucleotides as adjuvant [34].

Most bacteria require iron for survival, and while there is ample iron in the human body, it is sequestered and generally inaccessible to bacteria. Consequently, UPEC and many other pathogenic bacteria rely upon iron-chelating molecules and receptors that enable them to scavenge essential iron from the host [35]. Use of purified bacterial iron receptor proteins for vaccination against UPEC has had mixed results. Of 7 UPEC-associated iron receptors tested as vaccines in mice, 2 (IreA and LutA) provided significant protection against experimentally induced cystitis [36]. Vaccination with another iron receptor, Hma, protected against kidney infection, but not cystitis. For this analysis, the purified iron receptors were delivered intranasally after being conjugated to cholera toxin to increase antigenicity.

In total, these studies highlight both FimH and iron receptors as potentially valuable vaccine candidates that merit further investigation. However, as with mannosides and pilicides, the use of purified iron receptors, FimH, or other UPEC-associated factors as vaccines may have inadvertent effects on members of the endogenous microbiota that should be considered. In addition, the route of vaccine delivery and the types of adjuvants utilized need to be optimized for maximal efficacy in humans. While individuals prone to recurrent or chronic UTIs may benefit greatly from the development of anti-UPEC vaccines, the costs and risks of this strategy require further evaluation.

Despite these hurdles, initial success in the development of anti-UPEC vaccines has spurred the search for additional vaccine antigens. Candidate approaches, in which known virulence factors such as flagellin are targeted, continue to generate promising results [37], but less biased methods that are not necessarily reliant on our limited understanding of UTI pathogenesis may prove more fruitful. Along these lines, researchers have developed in silico approaches, known collectively as reverse vaccinology, to probe the increasingly large number of sequenced bacterial genomes for pathogen-specific, surface-localized antigens [38, 39]. These traits in a vaccine antigen should increase the efficacy of antibody responses while limiting cross-reactivity with nonpathogenic bacteria. This approach to vaccine design is encapsulated in a publicly available, Web-based system known as Vaxign (http://www.violinet.org/vaxign/). By screening for outer membrane proteins with amino acid sequences that are conserved among UPEC isolates, but absent from nonpathogenic *E. coli* strains as well as humans and mice, Vaxign identified 22 putative UPEC-specific vaccine targets [40]. Several of these are functionally undefined, and a few are known to be expressed by UPEC during UTI, but to date none have been shown to protect against cystitis. The refinement of reverse vaccinology, coupled with gene expression profiling, proteomic analyses, and emerging high-throughput genetic screens, promises to greatly enhance our ability to identify useful vaccine targets.

CONCLUSIONS

Although UTIs are often considered to be easily managed infections, they remain a huge burden for millions of individuals and our healthcare system. The increasing prevalence of antibiotic resistance among uropathogens presents a major challenge to the clinical management of UTIs. Recurrent infections, including those caused by antibiotic-sensitive pathogens, are exceptionally common and are likely attributable in part to the establishment of recalcitrant intracellular bacterial reservoirs within the bladder mucosa. Eradication of these clinically relevant reservoirs will require a better understanding of the underlying molecular mechanisms that allow for their persistence. The ongoing development of new antimicrobial approaches, such as the use of pilicides and mannosides in conjunction with antibiotics, will provide new treatment options, while the identification of new vaccine candidates and optimized vaccination protocols promises relief to individuals who suffer from recurrent or chronic UTI.

Notes

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