



Uropathogenic *Escherichia coli*

Christopher Duplessis, MD, MPH
 Tyler Warkentien, MD
 Mary Bavaro, MD

Infection of the urinary tract is a common complaint in female patients. This article discusses epidemiology and treatment, as well as prevention and screening options important for the ObGyn practitioner.

Christopher Duplessis, MD, MPH, is an Infectious Disease Fellow, **Tyler Warkentien, MD**, is an Infectious Disease Fellow, and **Mary Bavaro, MD**, is an Infectious Disease Staff Physician; all at the Infectious Disease Division, Naval Medical Center, San Diego, CA.

Urinary tract infections (UTIs) are among the most common bacterial infections in women; *Escherichia coli* is the most common pathogen.^{1,2} UTIs engender substantial morbidity as well as some mortality, exacting enormous health care costs. In recent years, an increasing number of *E coli* UTIs are caused by multidrug-resistant organisms. Drug resistance, such as extended-spectrum β -lactamase (ESBL)-producing organisms, make antimicrobial options limited. Concerted vigilance to infection control and antibiotic stewardship will become even more important to curtail this serious public health problem.

EPIDEMIOLOGY

The self-reported annual incidence of UTIs in women is 12%, with a peak incidence of 18.6% in women ages

20 to 24; there is minimal decline in incidence between 10% and 15% across all age-groups.³ About 40% to 50% of women experience UTI in their lifetime, and 25% to 33% report recurrence within 6 to 12 months.⁴ Finally, increasing age is a risk factor for UTI associated with ESBLs.⁵ UTIs account for 7 million office visits and more than 100,000 hospitalizations annually. Treatment comprises upward of 15% of physician prescriptions and more than \$1 billion in annual health care costs.⁶ Most infections are innocuous; however, potential complications include pyelonephritis and urosepsis.

UTI risk factors include extremes in age, female gender, bladder catheterizations, nephrostomy tubes, prior antibiotic administration, diabetes, mechanical obstructions, and anatomical abnormalities that promote urinary stasis (eg, neurogenic bladder, pregnancy, kidney stones). Women are at elevated risk due to the short distance between the anus and urethra, as well as a short urethra emptying the bladder.^{3,7}

Postmenopausal women are at particular risk for UTIs secondary to a decrease in estrogen that results in increased vaginal pH, vaginal atrophy, and depletion of lactobacillus, which ordinarily keeps the pH of the vagina low. Lower pH deters bacterial growth. Loss of lactobacillus results in a more favorable environment for colonization of the vagina with rectal organisms, and subsequent colonization of the urogenital tract.

Receipt of antibiotics eradicates normal commensal periurethral flora, again creating opportunities for colonization of less favorable pathogens. Behavioral risk factors remain controversial. Sexual intercourse may increase susceptibility, and particular practices (eg, anal intercourse, sex with uncircumcised partner) may incur greater risk of vaginal colonization with coliforms. Douching, use of menstrual sanitary napkins, and postevacuation wiping direction have failed to yield consistent correlations.⁶

UROPATHOLOGY

Strains of *E coli* that have a predilection for the urinary system are known as uropathogenic *E coli*. They have unique virulence factors that contribute to their ability to cause UTIs, including adhesion-promoting

structures (types 1 and P fimbriae), and toxins such as cytotoxic necrotizing factor and its polysaccharide coating. These virulence factors allow the organism to attach, invade, find nutrients, and evade the immune system.

Uropathogenic *E coli* possess fimbriae (fingerlike projections, also called pili) that bind to glycoproteins on uroepithelial cells through sites called adhesins. This attachment allows uropathogenic *E coli* to withstand being flushed by urine from the system.¹ These fimbriae are seldom identified in asymptomatic bacteriuria.⁶ After adherence, many pathogenic *E coli* secrete toxins to mediate further transmigration, including α -hemolysin (cytotoxic-necrotizing factor) and secreted autotransporter toxin, leading to cellular apoptosis or cell lysis. The hemolysin toxin is present in 50% of isolates responsible for pyelonephritis.⁶

HOST RESPONSE, DEFENSE, AND RISK FACTORS

The uroepithelial mucosal surface is lined with highly sulfated, anionic glycosaminoglycans contributing to bladder wall impermeability and resistance to microbial adherence.⁴ The flushing activity of urine alone serves to prevent microbial attachment. The kidneys secrete Tamm-Horsfall glycoprotein (THP, originally identified as an inhibitor of viral hemagglutination), which binds to *E coli* fimbriae, preventing microbial attachment to the bladder mucosa.⁸ In addition to serving in the capacity as a “sacrificial ligand,” THP appears to function as an immunoregulatory molecule activating dendritic cells.⁴

Uroepithelial cells may endocytose adherent bacteria, which bind to the uroplakins (mannosylated glycoproteins) on surface epithelium cells via type 1 fimbriae. After engulfing the bacteria, the urothelial cells may undergo apoptosis and sloughing; become hyperinfected, potentiating infection of neighboring cells; or harbor the bacteria in a dormant yet viable state poised for future recurrent UTIs, all predicated on the interplay between host defense apparatus and the microbial virulence factors.¹

Numerous innate and adaptive immune responses are necessary to combat UTIs. Toll-like receptors (TLRs) are pattern recognition receptors, which serve to activate the

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immune system upon exposure to microbes. Preservation of normal commensal flora is necessary to prevent the colonization of virulent microbes. The healthy premenopausal vagina primarily harbors lactobacilli, which can be bactericidal against other organisms by their secretion of hydrogen peroxide. Disturbance in lactobacilli colonization (spermicide use, postmenopausal hormonal alterations, or selective antibiotics) engenders increased colonization with uropathogenic *E coli*.²

TREATMENT

Treatment Guidelines

For uncomplicated UTIs, a 3-day course of trimethoprim-sulfamethoxazole (TMP-SMX) remains first-line therapy if the regional resistance pattern shows less than 20% resistance. Fluoroquinolones are acceptable alternatives if resistance to TMP-SMX exceeds 20%. However, fluoroquinolone resistance is increasing globally, with regional prevalences of 37% in Europe and 69% in India.⁹ Additionally, ESBL organisms invariably harbor numerous associated plasmid-mediated resistance genes, conferring resistance to fluoroquinolones.

Nitrofurantoin for 5 to 7 days is acceptable and may be effective against some ESBLs and vancomycin-resistant enterococci, but since blood levels are low, it should not be used in cases of pyelonephritis or bacteremia.¹⁰ Second-line agents include oral cephalosporins, doxycycline, amoxicillin, and amoxicillin/clavulanate. Chronic indwelling catheters associated with UTI mandate replacement, then urine culture to direct treatment, typically for 7 days.¹⁰

Asymptomatic bacteriuria should not be treated, except prior to urologic surgery with mucosal compromise or in pregnancy. Symptomatic or asymptomatic UTI in pregnancy presents the risk for pyelonephritis, which engenders increased morbidity for both mother and fetus. Thus, screening for UTI is warranted and recommended in pregnancy (optimally at 16 weeks), and treatment should be rendered if positive for bacteriuria, whether symptomatic or asymptomatic. Treatment regimens include penicillins, cephalosporins, and nitrofurantoin. Nitrofurantoin should be avoided late in pregnancy, given the risk

of fetal hemolytic anemia in patients with G6PD deficiency.⁶

Threat of Microbial Resistance

Since the 1990s, ESBLs in *E coli* and other enteric gram-negative rods have seriously hindered treatment options, while rates of complications, such as urosepsis, have risen.⁵ These organisms produce varying types of β -lactamases, rendering resistance to several antibiotic classes, including all the cephalosporins and aztreonam.

ESBL organisms often harbor resistance to multiple non- β -lactam antibiotics, including fluoroquinolones, TMP-SMX, tetracyclines, and gentamicin. In one study, resistance to ciprofloxacin and TMP-SMX occurred in 64% and 57% of ESBL isolates, respectively.¹¹ Of additional concern, one particular type of ESBL harbored by *E coli*—the CTX group—is becoming the source of true community-acquired infections.

Risk factors for ESBLs include recurrent UTIs, renal pathology, prior antibiotic administration (cephalosporins and fluoroquinolones), prior hospitalization, nursing home residency, older age, diabetes, and liver disease.¹² The drug of choice for treatment of infection with an ESBL organism is a carbapenem, a class that is not currently available in oral preparations. Carbapenems generally should be reserved for more severe infections.¹³ Some possible approaches to infection limited to the bladder are discussed below.

Fosfomycin

Fosfomycin is a broad-spectrum bactericidal oxirane antibiotic unrelated to other classes. It interferes with bacterial cell wall synthesis via a different mechanism than that of the β -lactams. Fosfomycin acts as an analog of phosphoenolpyruvate, inhibiting a key enzyme involved in peptidoglycan synthesis. It has been used extensively in France, Spain, Germany, and Japan and is available in the United States.¹⁴ It possesses a long half-life (5.7 ± 2.8 hours) and low molecular weight with good tissue penetration (including urinary tract), excreted unchanged in urine.

Fortunately, to date, the resistance to fosfomycin remains low. This is speculated to be because resistance mechanisms are chromosomally mediated, and thus less

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easily transferable, as with plasmid-mediated resistance genes. Additionally, given fosfomycin's unique mechanism of action, inhibiting a key enzyme upstream of cell wall-associated peptidoglycan synthesis, it is speculated that potential resistance mechanisms would incur a substantial biological and fitness cost, reducing the capacity for survival.¹⁴

Fosfomycin tromethamine is the soluble salt with improved bioavailability. It is approved for uncomplicated UTIs caused by *E coli* and *Enterococcus faecalis*. It is prescribed as 3 g in a single dose. Like nitrofurantoin, fosfomycin has no role in the treatment of pyelonephritis, given lack of sufficient concentration within the renal parenchyma or serum. Fosfomycin had 90% efficacy against all urinary isolates including methicillin-resistant *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Enterococcus*.¹⁵

Clavulanic Acid

Clavulanic acid is an effective ESBL inhibitor; however, amoxicillin/clavulanate and ticarcillin/clavulanate have fared poorly in clinical use for such infections.¹⁶ A novel strategy utilizing an oxyimino-cephalosporin and clavulanate combination nevertheless revealed efficacy against most ESBL-producing *E coli* and *Klebsiella* spp.¹⁶ Clavulanic acid with cefepime, cefpirome, or cefpodoxime can also overcome inducible AmpC production by *Enterobacter*.

Due to patent restrictions, and since the antibiotics are produced by several different companies, it is difficult to test the efficacy of various combinations as delineated above. Many of these restrictions are absent outside the United States. For example, trials exploiting cefpisome-tazobactam (tazobactam is another β -lactamase inhibitor) are being launched in India.

Recurrent UTIs:**Evaluation and Treatment**

Women with 3 or more UTIs in a year warrant urologic evaluation. This may encompass an exam to rule out pelvic and gynecologic abnormalities and radiographic and cystoscopic evaluation to assess anatomical abnormalities (eg, stones, diverticulum, malignancy, interstitial cystitis, ectopia). Postmenopausal women should

also have an evaluation of renal function and emptying.

In the absence of identifiable risk factors for recurrent infections, several prophylactic strategies are available for recurrent UTIs, including chronic low-dose antibiotics (nitrofurantoin, TMP), symptomatic treatment, and postcoital treatment. Options include use of nitrofurantoin at 50 or 100 mg daily or TMP-SMX at one-half strength tablet daily or every other day. Either of these medications can be used for 6 to 12 months, followed by a period off all antibiotics and a reevaluation for return of infection.

PREVENTION AND PROPHYLAXIS

Patients to be considered for preventive measures include women experiencing recurrent UTIs, children with structural abnormalities of the urinary tract or recurrent UTI, patients with spinal cord injury or neurogenic bladder, and patients after renal transplant.²

Cranberry Juice

Cranberry juice contains a tannin called A-type proanthocyanidin, a compound found in many plants that serves as an antimicrobial defense. It likely acts by decreasing microbial adherence of the P-fimbriae to the urothelium. Additionally, it is acidic, including a precursor of a known bacteriostatic agent (hippuric acid). To date, the evidence is controversial; nevertheless, some studies reveal efficacy.^{2,10}

Lactobacilli

Lactobacilli probiotic administration has many proposed mechanisms efficacious at decreasing UTIs, including elaboration of hydrogen peroxide, production of an acidic environment, and production of bacteriocidins and biosurfactants. Studies await demonstration of efficacy, as well as demonstration of adequate vaginal colonization after oral supplementation. To date there is no evidence for its benefit.¹⁰

Topical Estrogen

Topical estrogen is a reasonable treatment for postmenopausal patients with recurrent UTIs. Theoretically, it is thought to reestablish a vaginal acidic milieu and to reconsti-

tute premenopausal flora, including lactobacilli.^{6,10} However, studies are conflicting on the efficacy of oral or topical estrogen therapy in preventing recurrent UTIs.

Methenamine Hippurate

Another potential strategy to prevent UTIs involves the use of methenamine hippurate. Methenamine hippurate is hydrolyzed to formaldehyde and ammonia in acidic urine. Formaldehyde has nonspecific bactericidal action, and hippuric or mandelic acid aids in maintaining the requisite urine acidity, in addition to suppressing bacteria. This drug may have efficacy in prevention and treatment of UTIs in patients without renal tract abnormalities. It does not appear efficacious in those with neurogenic bladder or renal tract abnormalities. It has low risks for adverse events.¹⁷ To ensure an acidified urine, it may be combined with cranberry juice or vitamin C.

SCREENING

Pregnancy is the only condition for which asymptomatic UTI screening is recommended, as subsequent infection is known to engender adverse sequelae to the newborn. No data exist to support screening in otherwise asymptomatic individuals, including those with diabetes and neurogenic bladder, the elderly, and those who are catheterized.³ In such patients, symptomatic episodes are not decreased, and treating bacteriuria risks adverse effects and causing increasingly resistant organisms.¹⁰ Upward of 20% of women older than 80 will possess asymptomatic bacteriuria, and no data support treatment in this population either.¹⁰ Symptomatic infection must prompt urinary cultures to direct appropriate therapy.¹⁰

CONCLUSION

The advent of increasing resistance to antimicrobials without foreseeable novel antimicrobial therapeutics in the near future mandates innovative strategies to treat *E coli* UTIs. Continued research evaluating the roles of receptors, signaling molecules, cytokines, and regulation of the immune system will be important as we search for a potential vaccine. Expectations are that our current antimicrobials will become less ef-

fective against these ESBL-producing *E coli* strains.

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