Urinary Tract Infection
Antimicrobial Susceptibility Testing

Urinary Tract Infections (UTIs) are a major source of morbidity in the United States. Community-acquired UTIs largely affect women of reproductive age, with 11% of women experiencing one episode each year, one-third of women having one episode by the age of 26, and 60% experiencing at least one during their lifetime [1]. In 1997, these infections resulted in 7 million physician office visits and 1 million emergency room visits [2]. Estimated treatment costs of these infections was $1.6 billion in 1995 [1], which is the equivalent of $2.2 billion in inflation-adjusted 2009 dollars. UTIs are defined clinically by the presence of a significant level of bacteria in the urine (i.e., bacteriuria). Guidelines vary, but typically a pure culture of between 10^4-10^6 colony forming units (CFUs) / milliliter (mL) of urine is indicative of a UTI. Patient symptoms include painful, urgent and frequent urination, along with malodorous and/or cloudy urine. Signs of infection include the presence of blood (hematuria) or white blood cells (pyuria) in the urine.

UTIs comprise a spectrum of diseases of varying severity, with different outcomes and treatment guidelines. Asymptomatic infections are referred to as asymptomatic bacteriuria (ABU), whereas symptomatic infections are classified as either cystitis (confined to the bladder) or pyelonephritis (infection has spread to the kidneys). Due to the absence of symptoms, ABU is often only discovered through a positive urine culture and does not require treatment unless risk factors for complication are present (e.g., pregnancy, kidney transplantation). Cystitis is normally treated as an out-patient procedure with oral antimicrobial therapy, although recurrence is a major problem, with 27% of patients experiencing another episode within 6 months and 44% experiencing another episode within 1 year [3, 4]. In addition to the symptoms of cystitis, pyelonephritis is characterized by fever, flank pain and vomiting. Pyelonephritis is a serious and potentially life-threatening condition that frequently results in hospitalization—nearly 200,000 such cases were reported in the United States in 1997 [5]. Pyelonephritis patients are also at very high risk of developing sepsis (i.e., urosepsis), and 25% of all sepsis cases originate from a UTI [6]. *Escherichia coli* is responsible for >80% of community-acquired UTIs, with most other infections caused by *Staphylococcus saprophyticus*, *Klebsiella* spp., *Proteus mirabilis* and *Enterococcus faecalis* [7].

Community-acquired symptomatic UTIs are normally treated with empirical antimicrobial therapy upon diagnosis, whereas ABU is often left untreated unless the case is complicated (e.g., pregnancy, kidney transplantation). The recommended first-line antibiotic therapy for cystitis is a 3-day course of trimethoprim-sulfamethoxazole (SXT). Trimethoprim and sulfamethoxazole are both bacteriostatic inhibitors of the folate pathway required for bacterial synthesis of thymidine. With regards to β-lactam antibiotics, penicillins, ampicillin, amoxicillin, and some cephalosporins are not recommended for treatment since resistance is prevalent among UPEC due to expression of β-lactamases. A combination of a β-lactam with a β-lactamase inhibitor such as amoxicillin-clavulanic acid can be used to overcome β-lactamase production. In geographic areas where UPEC resistance to SXT exceeds 15% to 20%, a 3-day course of a fluoroquinolone such as ciprofloxacin is recommended for non-pregnant women. As fluoroquinolones and trimethoprim are assigned to the FDA pregnancy risk “C” category (gestational risk in animal studies and no adequate human studies), pregnant patients are prescribed a 7-day course of nitrofurantoin, which in its reduced form damages bacterial DNA. Pyelonephritis is more aggressively treated with 14-day courses of paranteral broad spectrum antibiotics, either fluoroquinolones or cephalosporins (second or third generation) [8].

Although current therapies are effective, the increasing prevalence of antimicrobial resistance amongst UTIs is a major issue. The North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study analyzed resistance among 1,142 UPEC isolates from outpatients at 40 medical centers and found resistance rates of 21% to SXT and 5% to 6% to fluoroquinolones [9]. A similar study in European and South American nations collected 2,315 UPEC isolates and determined that 29% were resistant to SXT and 8% were resistant to ciprofloxacin [10]. The high level of SXT resistance has forced a switch to fluoroquinolones as a front-line therapy in many areas, with predictable consequences. Between 1998 and 2005, a four-fold increase in levofloxacin prescriptions for UTIs at one medical center was correlated with an increase in resistance from 1% to 9% [11]. Another study, analyzing 11,407 UPEC isolates from outpatients, determined that the prevalence of extended-spectrum β-lactamases (ESBLs), capable of hydrolyzing third generation cephalosporins (e.g. ceftriaxone, ceftazidime), increased from 0.21% in 2003 to 3% in 2008 [12].

Medical Diagnostic Laboratories, L.L.C. (MDL) is now offering antimicrobial susceptibility testing available from the *UroSwab*® specimen collection platform for specimens submitted for the detection of *E. coli*, *Klebsiella* species or *P. mirabilis*. The antibiotics delineated herein are indicated for the treatment of uncomplicated cystitis. Urethritis may be due to sexually transmitted organisms and pyelonephritis may require additional medical considerations. A positive PCR test for any of these three bacteria is a prerequisite for performing these UTI antimicrobial susceptibility tests.

Amoxicillin/Clavulanic Acid

Amoxicillin is a β-lactam antibiotic that inhibits bacterial cell wall synthesis. However, β-lactamases, which hydrolyze amoxicillin, are highly prevalent among uropathogens. Therefore, amoxicillin is prescribed in combination with clavulanic acid, a β-lactamase inhibitor, which restores
the antimicrobial activity of amoxicillin against β-lactamase-expressing pathogens. However, some uropathogens express inhibitor-resistant β-lactamases, as evidenced by a recent international study finding that 3.8% of UPEC isolates were resistant to amoxicillin/clavulanic acid [10].

Cephalothin (similar to Keflex)

Cephalothin is a 1st generation parenteral cephalosporin β-lactam antibiotic with a similar antimicrobial spectrum to cefazolin and cephalaxin, and is used to predict the activity of oral cephalosporins cephalaxin, cefadroxil, cefaclor, and cephadrine as recommended by the Clinical and Laboratory Standards Institute (CLSI). Similar to amoxicillin, this antibiotic inhibits bacterial cell wall synthesis. Resistance is rare, with <1% of UPEC isolates exhibiting inhibitor-resistant β-lactamases (ESBLs). Resistance among uropathogens is rare, but emerging, with 3% of UPEC isolates reported to be resistant in 2008 [12].

Trimethoprim/Sulfamethoxazole

Trimethoprim and sulfamethoxazole are inhibitors of folate synthesis which block bacterial DNA replication. They exhibit synergistic activity in vitro, and are prescribed in a 1:5 ratio. Resistance is mediated by acquisition of genes that encode inhibitor-resistant folate synthesis enzymes. A large study of outpatients in North America found that 21% of UPEC isolates were resistant to trimethoprim/sulfamethoxazole [9]. Current guidelines recommend avoiding the use of this drug as a front-line therapy in geographic areas where resistance exceeds 15% [8].

Nitrofurantoin

Nitrofurantoin is an antibiotic for E. coli and S. saprophyticus that works by damaging bacterial DNA. It is often recommended for treatment of pregnant women, for whom fluoroquinolones (e.g., ciprofloxacin) and trimethoprim are contra-indicated since they are assigned to FDA Category C (gestational risk in animal studies and no adequate human studies). Nitrofurantoin is not recommended for women who are in their last month of pregnancy, are nursing, or have kidney disease. Only 1.1% of UPEC isolates are reported as being resistant to this drug [9].

Ciprofloxacin

Ciprofloxacin is a fluoroquinolone antibiotic that inhibits bacterial gyrase, an enzyme required for DNA replication. Resistance is mediated by mutations in the gene encoding gyrase that results in expression of an inhibitor-resistant enzyme. 5.5% of UPEC isolates in North America are reported to be resistant [9]. CLSI also uses Ciprofloxacin to predict the activity of Levofloxacin.

Fosfomycin

Fosfomycin is an inhibitor of bacterial cell wall synthesis indicated for E. coli only, as recommend by the CLSI. Resistance is rare, with <1% of UPEC isolates exhibiting resistance in a recent large international study [10]. Although not commonly prescribed, fosfomycin is beginning to emerge as an alternate therapy, especially for ESBL-expressing uropathogens [13]. Fosfomycin is prescribed as a single dose for pregnant women.

REFERENCES: