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Antibiotic Resistance in Urinary Tract Infections: Current Issues and Future Solutions

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1. Introduction

1.1 Incidence and costs

UTIs are a major source of morbidity and associated healthcare costs in the United States (US). Community-acquired UTIs largely affect women of reproductive age, with 11% of women experiencing infections each year, one-third of women having an infection by the age of 26, and 60% experiencing at least one infection during their lifetime (Foxman *et al*., 2000). In 1997, the last year for which epidemiological data is available, these infections resulted in 7 million physician office visits and 1 million emergency room visits (Foxman, 2002). Treatment of these infections cost $1.6 billion in 1995 (Foxman et al., 2000), which is the equivalent of $2.2 billion in inflation-adjusted 2009 dollars. UTIs are also a major health problem for hospitalized patients, especially those undergoing long-term catheterization. Catheter-associated UTIs account for >40% of nosocomial infections, with over 1 million cases per year at a cost of $451 million (Jacobsen *et al*., 2008).

1.2 Diagnosis

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 are 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 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 if they are confined to the bladder or pyelonephritis if the infection has spread to the kidneys. Due 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). Most catheter-associated nosocomial UTIs can be categorized as ABU, since the presence of a urinary catheter obscures patient symptoms. Cystitis is normally treated on an out-patient basis 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 (Foxman, 1990, Ikaheimo *et al*., 1996). 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 in were reported in the US in 1997 (Foxman *et al*., 2003). Pyelonephritis patients are at very high risk of developing sepsis (i.e. urosepsis), and 25% of all sepsis cases originate from a UTI (Wagenlehner *et al*., 2008).

1.3 Etiology

The source of UTI pathogens is generally considered to be the patient's own flora. UTIs are preceded by colonization of the vagina and periurethral area by uropathogens from the GI tract (Hilbert, 2011). Women are much more susceptible than men to community-acquired UTIs, in part, due to the female anatomy in that a much shorter urethra allows pathogens easier access to the bladder. Uropathogenic *Escherichia coli* (UPEC) is responsible for >80% of community-acquired UTIs, with most other infections caused by *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterococcus faecalis* (Ronald, 2003). UPEC is the cause of between one-third and one-half of all nosocomial UTIs, which in addition to the previously mentioned uropathogens, are also caused by *Enterobacter* spp., *Pseudomonas aeruginosa*, Group B streptococci and fungal pathogens (e.g. *Candida* spp.) (Mathai *et al*., 2001, Gordon & Jones, 2003, Hidron *et al*., 2008). Eighty percent of nosocomial UTIs are catheter-associated, as insertion of the catheter introduces fecal microbes and genital flora into the urinary tract (Jacobsen et al., 2008).

2. Treatment

2.1 Community-acquired UTIs

Community-acquired symptomatic UTIs are treated with empirical antimicrobial therapy upon diagnosis based on patient symptoms. Urine cultures are recommended for complicated and recurrent cases, and may be performed for uncomplicated cases, although physician guidelines vary. Since treatment will precede identification of the pathogen, local trends for antibiotic resistance must be accounted for. The recommended first-line antibiotic therapy for cystitis is either 100 milligrams (mg) of nitrofurantoin per day for 5 days or 160 mg-800 mg of trimethoprim-sulfamethoxazole (SXT) per day for 3 days. Nitrofurantoin should be avoided if pyelonephritis is suspected, as this drug only reaches an effective concentration in the bladder. SXT should be avoided if resistance in the area is >20% or if the patient has been treated with this antibiotic in the last three months. Another option for treatment is Pivmecillinam (400 mg daily for 3-7 days), but this drug is not approved for use in North America and some European countries. Fosfomycin (3 gram single dose) can also be used, but some studies suggest it is less effective than nitrofurantoin or SXT. Although amoxicillin and ampicillin should be avoided due to endemic resistance, 3-7 day courses of the β-lactam-β-lactamase inhibitor combination amoxicillin-clavulanic acid, as well as cephalosporins such as cefaclor, cefdinir and cefpodoxime proxetil, may be used. However, they exhibit less effectiveness and are associated with more adverse effects than the recommended front-line therapies (nitrofurantoin and SXT). Fluoroquinolones (e.g. ciprofloxacin, ofloxacin and levofloxacin) are highly effective in 3-day courses, resistance is minimal and they are well-tolerated, but are only recommended as second-line therapies as they are highly useful for more serious infections and their judicious use will delay the rise

of resistance. Pyelonephritis is a much more serious conditions, often requiring hospitalization and paranteral administration of antibiotics—either ceftriaxone (400 mg) or a consolidated twenty-four hour dose (i.e. 7 mg drug/kg body weight) of an aminoglycoside (gentaminicin or tobramycin), in addition to oral ciprofloxacin (Gupta *et al.*, 2011).

2.2 Pregnant patients

Although pregnant women are not at an increased risk for UTIs in general, they are more likely to develop pyelonephritis than non-pregnant women. Approximately 4-6% of both pregnant and non-pregnant women exhibit ABU. For otherwise healthy non-pregnant women, there is no need for treatment. However, if ABU is left untreated during pregnancy, 20-40% of these women will develop pyelonephritis, often during the third trimester (Macejko & Schaeffer, 2007). As a consequence, The American College of Obstetricians and Gynecologists recommends screening for ABU in all pregnant women at sixteen weeks of gestation (Millar & Cox, 1997), and patients with positive cultures should be treated. The most important consideration in treatment is that it must be safe for both mother and fetus. Therefore, fluoroquinolones and trimethoprim should not be used, as they are assigned to the US Food and Drug Administration (FDA) pregnancy risk "C" category (gestational risk in animal studies and no adequate human studies performed). As with non-pregnant patients, nitrofurantoin can be used as a front-line therapy. As noted previously, nitrofurantoin is not recommended for treatment of pyelonephritis due to poor tissue penetration. Patients should have a follow-up urine culture one week later to determine if treatment was successful, as 20-30% of patients will require additional treatment. In addition, up to one-third of pregnant women will suffer a recurrent infection during pregnancy. Therefore, after the initial episode, either administration of prophylactic antimicrobial therapy (50-100 mg of nitrofurantoin nightly) or frequent urine cultures should be performed throughout the pregnancy (Macejko & Schaeffer, 2007). Any pregnant patient who develops pyelonephritis should be admitted and treated with paranteral antimicrobial therapy (see above). Complications of pyelonephritis during pregnancy include low fetal birth weight and neonatal death, as well as maternal anemia, hypertension, renal failure and sepsis.

2.3 Catheter-associated UTIs

Nosocomial UTIs are usually associated with catheterization, and asymptomatic infections are not normally treated unless additional complications are present. For symptomatic patients, the recommended procedure is replacement of the catheter combined with a 7-14 days of treatment with an agent to which the pathogen is susceptible (e.g. SXT). Specifically, it has been found that a 5-day course of levofloxacin (oral or paranteral) is an appropriate treatment for patients who are not severely ill. Unlike community-acquired UTIs, culturing of a urine sample to identify the uropathogen and determination of antimicrobial sensitivities is recommended prior to treatment, due to the diversity of nosocomial uropathogens and high rates of resistance (Hooton *et al.*, 2010).

3. Antimicrobial resistance

3.1 Uropathogenic *E. coli* (UPEC)

3.1.1 β-lactam antibiotics

β-lactams antibiotics are the oldest and most broadly used class of antibiotics. They exert a bactericidal effect by inhibiting bacterial cell wall synthesis and are administered both orally

and parenterally to treat a wide variety of bacterial infections. These antibiotics fall into three major structural categories—penicillins, cephalosporins and carbapenems. Penicillins, such as ampicillin and amoxicillin, were used previously as front-line therapies for UTIs. Resistance to these agents is mediated by β-lactamases which degrade them, and these enzymes play an important role in antibiotic-refractory UTIs. The TEM, SHV and OXA classes of β-lactamases hydrolyze penicillin β-lactam antibiotics (e.g. amoxicillin) and are widely distributed among UPEC (Simpson *et al.*, 1980), resulting in 38-48% of these isolates being ampicillin-resistant (Schito et al., 2009, Zhanel et al., 2006). The genes encoding these β-lactamases are usually found on plasmids that are horizontally transferred between bacteria. Penicillin β-lactam resistance can be overcome by combining the penicillin β-lactam with a β-lactamase inhibitor, such as ampicillin-sulbactam, amoxicillin-clavulanic acid or piperacillin-tazobactam. However, inhibitor-resistant TEM β-lactamases have evolved, leading to emerging UPEC resistance—the Antimicrobial Resistance Epidemiological Survey (ARESC) of nine European countries and Brazil collected 2,315 UPEC isolates and found that 3.8% were resistant to amoxicillin-clavulanic acid (Schito et al., 2009). Similarly, the SENTRY antimicrobial resistance surveillance program analyzed 1,316 nosocomial UPEC isolates in North America, Latin America and Europe and found 5% resistance to this combination (Gordon & Jones, 2003). Mutant TEM and SHV β-lactamases have emerged that hydrolyze not only penicillins but also third-generation extended-spectrum cephalosporin β-lactam antibiotics (e.g. ceftriaxone). These enzymes are referred to as extended-spectrum β-lactamases (ESBLs). UPEC resistant to cerufoxime, and therefore expressing ESBLs, are responsible for 2.4% of community-acquired infections and 4% of nosocomial infections (Schito et al., 2009, Gordon & Jones, 2003). In addition, the US National Healthcare Safety Network analyzed 2,009 UPEC isolates from catheter-associated UTIs and found that 5.5% of isolates expressed ESBLs (defined by resistance to ceftriaxone or ceftazidime) (Hidron et al., 2008). Another class of β-lactamases is CTX-M, which originated by horizontal transfer of a chromosomal β-lactamase gene from the non-pathogenic genus *Kluyvera*. The epidemic UPEC clone O25:H4-ST131 encodes CTX-M-15, rendering it cephalosporin-resistant (Nicolas-Chanoine *et al.*, 2008). The most recent evolution in β-lactam resistance is the emergence of carbapenemases, enzymes that hydrolyze carbapenem of β-lactam antibiotics, which are resistant to degradation by other ESBLs. Carbapenemases are already a problem among catheter-associated UTIs, with 4% of isolates resistant to imipenem, meropenem or ertapenem (Hidron et al., 2008). In addition, the New Delhi metallo--β-lactamase-1 (NDM-1) carbapenemase, has been identified in a O25:H4-ST131 UPEC isolate (Peirano *et al.*, 2011). Although β-lactam-β-lactamase inhibitor combinations, cephalosporins and carbapenems remain effective for UTI treatment, epidemiological trends suggest that emerging resistance will be problematic. For example, a study analyzing 11,407 UPEC isolates from community-acquired infections determined that the prevalence of ESBLs increased from 0.21% in 2003 to 3% in 2008 (Qi et al., 2010).

3.1.2 Trimethoprim-sulfamethoxazole (SXT)

Trimethoprim and sulfamethoxazole are both inhibitors of bacterial folate synthesis, which is required for *de novo* synthesis of thymidine, and therefore DNA synthesis. They are administered orally in combination as a 1:5 ratio (SXT). Traditionally a front-line therapy for UTIs, their utility has decreased in certain areas due to increasing resistance. In general, guidelines state that SXT should be avoided once resistance reaches 15-20%(Gupta et al.,

2011). 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 that 21% were resistant to SXT (Zhanel et al., 2006). Similarly, the ARESC study found that 29% of UPEC isolates were resistant (Schito et al., 2009). Trimethoprim and sulfamethoxazole inhibit dihydrate folate reductase, and dihydropteroate synthetase, respectively, and resistance to SXT can be mediated by horizontal transfer of genes encoding resistant versions of these enzymes. A study of 305 SXT-resistant UPEC isolates found that 66% of them encoded a *dfr* allele encoding a trimethoprim-resistant dihydrate folate reductase, and 96% of them had a *sul* gene encoding a sulfamethoxazole-resistant dihydropteroate synthetase. The presence of these genes on integrons and plasmids facilitates their spread among bacterial populations (Blahna *et al.*, 2006).

3.1.3 Fluoroquinolones

Fluoroquinolones, such as ciprofloxacin and levofloxacin, target bacterial DNA gyrase and topoisomerases, enzymes responsible for DNA unwinding during DNA replication. They are currently recommended for use as second-line agents for uncomplicated UTIs, and front-line therapy for nosocomial UTIs and pyelonephritis (Gupta et al., 2011, Hooton et al., 2010). Resistance to these agents is largely due to mutations in the *gyrA* gene encoding the gyrase enzyme. (Weigel *et al.*, 2002). The NAUTICA, ARESC and SENTRY studies reported UPEC resistance rates of 5-6%, 8% and 11%, respectively (Gordon & Jones, 2003, Schito et al., 2009, Zhanel et al., 2006). Alarmingly, 25% of UPEC from catheter-associated UTIs are fluoroquinolone-resistant (Hidron et al., 2008). The rate of UPEC fluoroquinolone resistance appears to be increasing rapidly. 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% (Johnson *et al.*, 2008). Similarly, a comparison of 2073 nosocomial UPEC isolates from 1990-1994 to 3112 isolates from 2000-2004 found that resistance to ciprofloxacin increased from 0.9% to 9.8% (Klevens *et al.*, 2008).

3.1.4 Nitrofurantoin

Nitrofurantoin is currently recommended as a front-line agent for the treatment of community-acquired cystitis (Gupta et al., 2011). The NAUTICA and ARESC studies of community-acquired UTIs found only 1.1% and 1.6% of UPEC isolates were nitrofurantoin resistant, respectively (Schito et al., 2009, Zhanel et al., 2006). Nitrofurantoin is a pro-drug, and when reduced it becomes highly reactive, damaging bacterial DNA. A laboratory study identified mutations in the nitroreductase-encoding genes *nsfA* and *nsfB* that led to resistance. However, the presence of these mutations was associated with poor bacterial growth, thus explaining why they are not commonly identified in resistant clinical isolates (Sandegren *et al.*, 2008). Nitrofurantoin is often recommended for treatment of pregnant patients, as there are concerns about the safety of fluoroquinolones and trimethoprim for this population (Macejko & Schaeffer, 2007). However, it is important to note that nitrofurantoin is not useful for the treatment of pyelonephritis, and also that many uropathogens other than *E. coli*, such as *K. pneumoniae*, *P. mirabilis* and *P. aeruginosa*, are non-susceptible.

3.1.5 Fosfomycin

Fosfomycin is a broad-spectrum *Streptomyces*-produced antibiotic that inhibits bacterial cell wall synthesis, and is currently recommended as a front-line therapy for community-

acquired UTIs (Gupta et al., 2011). *In vitro* studies found high rates of spontaneous resistance, but these mutants grew poorly, suggesting that clinical resistance should be rare (Nilsson *et al*., 2003). Indeed, the ARESC study found that only 0.6% of UPEC isolates were resistant (Schito et al., 2009). In addition, a recent meta-study analyzing 1657 ESBL-producing *E. coli* isolates, most of which were UPEC, found that 97% of them were susceptible to fosfomycin (Falagas *et al*., 2010). Therefore, fosfomycin may have significant utility in combating emerging UPEC antibiotic resistance.

3.1.6 Multi-drug resistant UPEC clones

In addition to general trends of increasing antibiotic resistance, specific multidrug-resistant UPEC clones have emerged. A year-long outbreak of O15:K52:H1 *E. coli* occurred in London in 1986-7, causing up to 13% of UTIs in this area during this time period. Most of these isolates were resistant to SXT, ampicillin, chloramphenicol, streptomycin and tetracycline (Phillips *et al*., 1988, O'Neill *et al*., 1990). Analysis of 100 different O15:K2:H1 clones, isolated over a span of 30 years, revealed that SXT resistance first emerged in this lineage in 1986 and fluoroquinolone resistance in 1995 (Olesen *et al*., 2009). A separate group of isolates (also related to O:15:K2:H1), termed clonal Group A (CGA), accounted for 50% of SXT-resistant, and 11% of total, cystitis isolates from three geographically distinct sites in the US. These isolates typically had similar O (lipopolysaccharide) antigens, encoded similar virulence factors and were frequently multidrug resistant (Manges *et al*., 2001). CGA isolates also comprise 34% of SXT-resistant, and 7% of total, SXT-resistant pyelonephritis isolates (Johnson *et al*., 2002). The third major antibiotic-resistant UPEC clone is O25:H4-ST131, which expresses the CTX-M-15 ESBL rendering it resistant to third-generation cephalosporins (Nicolas-Chanoine *et al*., 2008). These three clonal groups accounted for 37% of total UPEC isolates, 44% of SXT-resistant isolates and 64% of fluoroquinolone-resistant isolates in Canada from 2002-4 (Johnson *et al*., 2009). One-third of ciprofloxacin-resistant UPEC clones in a European study belonged to the O15:K2:H1 or O25:H4-ST131 groups (Cagnacci *et al*., 2008). There are also reports that the O25:H4-ST131 lineage has acquired the NDM-1 carbapenemase (Peirano et al., 2011) in North America and fosfomycin resistance in Spain (Oteo *et al*., 2009), indicating that this lineage will continue to evolve multi-drug resistance and be a major public health issue.

3.2 Resistance of other uropathogens

3.2.1 *Staphylococcus saprophyticus*

S. saprophyticus is a responsible for 2-6% of uncomplicated UTIs (Kahlmeter, 2003, Schito et al., 2009). The ARESC study found resistance rates of 36% for ampicillin and 10% for SXT (Schito et al., 2009). An earlier study analyzing isolates from sixteen European countries and Canada obtained different results, with only 2% of isolates resistant to ampicillin and none resistant to SXT (Kahlmeter, 2003). However, both studies found that >99% of isolates were sensitive to amoxicillin-clavulanic acid.

3.2.2 *Klebsiella pneumoniae*

K. pneumoniae is responsible for 1-6% of uncomplicated UTIs (Kahlmeter, 2003, Schito et al., 2009). In addition to being intrinsically resistant to ampicillin and nitrofurantoin, resistance to other antibiotics is very common among these isolates. One study found non-

susceptibility rates to be 23% for SXT, 21% for cefuroxime (a second-generation cephalosporin), 12% for fosfomycin and 6% for ciprofloxacin (Schito et al., 2009). An earlier study found a similar resistance pattern, although overall prevalence was lower (Kahlmeter, 2003). In both studies, 94-99% of isolates were susceptible to ciprofloxacin and 91-96% were susceptible to amoxicillin-clavulanic acid. In addition, *K. pneumoniae* is the cause of 8-11% of nosocomial catheter-associated UTIs, and 17-21% of these isolates are resistant to extended-spectrum cephalosporins and 10% are resistant to carbapenems (Hidron et al., 2008, Gordon & Jones, 2003).

3.2.3 *Proteus mirabilis*

P. mirabilis is the cause of 3-5% of uncomplicated UTIs. *P. mirabilis* is intrinsically non-susceptible to nitrofurantoin, and also has high levels of non-susceptibility to other common UTI therapies—15-38% for SXT, 16-33% for ampicillin and up to 14% for fosfomycin and 10% for ciprofloxacin. The lowest levels of non-susceptibility were observed for amoxicillin-clavulanic acid (1-6%) and first (cefadroxil) or second generation (cefuroxime) cephalosporins (4-7%) (Schito et al., 2009, Kahlmeter, 2003). *P. mirabilis* is also the cause of 5% of nosocomial UTIs and 10%of catheter-associated UTIs (Gordon & Jones, 2003, Hidron et al., 2008); however, no extensive studies of antimicrobial resistance for these isolates has been performed

3.2.4 *Enterococcus* spp.

Enterococcus spp. are responsible for 13% of nosocomial UTIs. Resistance rates were found to be 5% for vancomycin, 12% for ampicillin and ampicillin-clavulanic acid, 37% for SXT and 50% for ciprofloxacin. Only 1% of isolates were resistant to nitrofurantoin (Gordon & Jones, 2003). A study of catheter-associated UTIs in the US found that 15% of them were due to *Enterococcus* spp., and these isolates exhibited a much higher rate of vancomycin resistance (29%) than nosocomial isolates in general (5%). Most of the resistance was due to *E. faecium*, which was only responsible for 24% of infections but accounted for 72% of vancomycin-resistant isolates. In addition, 89% of catheter-associated UTI *E. faecium* isolates were ampicillin-resistant. In contrast only 6% of *E. faecalis* isolates were vancomycin-resistant and only 3% were ampicillin resistant (Hidron et al., 2008).

3.2.5 *Pseudomonas aeruginosa*

P. aeruginosa accounts for 8% of nosocomial UTIs, and is intrinsically resistant to ampicillin,, ampicillin-clavulanic acid, SXT, nitrofurantoin and cefuroxime. In addition, 59% of isolates were ciprofloxacin-resistant (Gordon & Jones, 2003). Ten percent of catheter-associated UTIs are caused by *P. aeruginosa*, and resistance rates were found to be 34% for fluoroquinolones, 25% for carbapenems (imipenem and meropenem), 11-13% for cephalosporins (cefepime and ceftazidime), and 17% for piperacillin (extended-spectrum β-lactam), alone or in combination with tazobactam (a β-lactamase-inhibitor) (Hidron et al., 2008).

3.3 Newer UTI therapies

3.3.1 Recently approved therapies

Doripenem is a broad-spectrum injectable carbapenem β-lactam, approved by the FDA in 2007 for treatment of complicated UTIs, including pyelonephritis. Analysis of 1,772 clinical

E. coli isolates (many from complicated UTIs) found that 99.8% of them were susceptible to doripenem, including all 30 ESBL-producers (Pillar *et al.*, 2008). Analysis of 6 Phase III clinical trials demonstrated that doripenem was as effective as levofloxacin, imipenem, meropenem and piperacillin-tazobactam in treatment of patients with complicated UTIs due to ciprofloxacin-resistant and ESBL-producing *Enterobacteriaceae* (largely UPEC) (Kaniga *et al.*, 2010). Prulifloxacin is a fluoroquinolone approved for treatment of UTIs in Italy and Japan, but not yet approved in the US. A study of 257 patients with complicated UTIs showed it was as effective as ciprofloxacin (Carmignani *et al.*, 2005).

3.3.2 Clinical therapeutic candidates

ACHN-490 is a next-generation therapeutic belonging to the aminoglycoside family of antibiotics that inhibit bacterial protein synthesis. It has demonstrated efficacy *in vitro* against carbapenemase-expressing *E. coli* and *K. pneumoniae* (with the exception of NDM-1-expressing isolates) (Livermore *et al.*, 2011). It is currently being evaluated in a Phase II clinical trial for treatment of complicated UTIs. NXL104 is a novel inhibitor of CTX-M β-lactamases (Livermore *et al.*, 2008), and patients are being recruited for a Phase II trial to test its efficacy as a combination therapy with ceftaroline (fifth-generation cephalosporin) for the treatment of complicated UTIs. There is anecdotal evidence that tigecycline, a glyclcycline bacterial protein synthesis inhibitor, may be useful in treating complicated UTIs due to multi-drug resistant UPEC (Geerlings *et al.*, 2010). Although tigecycline is not approved for treatment of complicated UTIs, it has been suggested that it should be evaluated for this indication (Bhattacharya *et al.*, 2009)

3.3.3 Experimental therapies

A number of other compounds are still being developed experimentally, and although far from the clinic, they provide promise as potential future therapies. One new approach to treating UPEC infections is rather than attempting to prevent growth or kill the pathogen, is instead to inhibit its virulence properties so that an infection cannot persist (i.e. antivirulence therapies). This approach has focused on type 1 fimbriae that are required by UPEC to adhere to the bladder epithelium during infection (Hilbert, 2011). The FimH adhesin of type 1 fimbriae normally binds mannose, and related compounds, such as butyl α-D-mannoside, bind with much higher affinity, and therefore may be useful as decoys to saturate FimH and impair UPEC adherence to the bladder epithelium (Bouckaert *et al.*, 2005). Type 1 fimbriae are assembled through the chaperone-usher pathway, and ring-fused 2-pyridone peptidomimics (i.e. pilicides) impair this pathway, thereby preventing fimbrial expression, bacterial adherence and virulence in a mouse model of infection (Pinkner *et al.*, 2006, Klein *et al.*, 2010). Future studies are necessary to determine if antivirulence therapies will be useful in the clinic.

4. Prevention

4.1 Cranberry juice

In addition to improving therapy, another major area of research is the prevention of UTIs. As is the case for treatment, both traditional and novel strategies are being evaluated. Consumption of cranberry juice is a traditional folk method of UTI prevention and treatment. Roughly a dozen studies have been performed examining the ability of cranberry

products to prevent UTIs (Raz *et al*., 2004), but only two were randomized placebo-controlled studies with significant patient populations (150 women with a history of UTI). One study found that daily consumption of cranberry juice concentrate reduced the risk of UTI to 16% over a six month period, compared to 36% in the placebo group. A one-year study found that <20% of women who consumed cranberry juice or tablets experienced UTIs, compared to 32% in the placebo group (Kontiokari *et al*., 2001, Stothers, 2002). As for the mechanism of action, studies have found that cranberry juice extracts inhibited the ability UPEC to adhere to vaginal and bladder epithelial cells (Hilbert, 2011). Identification of the inhibitory cranberry constituent could facilitate the development of a novel antivirulence therapy for UTIs.

4.2 Vaginal probiotics

As vaginal and periurethral colonization with UPEC is strongly associated with UTIs (Hilbert, 2011), another prevention strategy is to use vaginal probiotics to prevent colonization. Small pilot studies have found that vaginal colonization with *Lactobacillus* spp. helps to prevent recurrent UTIs (Bruce & Reid, 1988, Uehara *et al*., 2006, Reid *et al*., 1992). A Phase I trial on the use of vaginal *Lactobacillus* suppositories to prevent recurrent UTIs has been completed with minimal patient side effects (Czaja *et al*., 2007), paving the way for future trials and the possible use of probiotics clinically to prevent UTIs.

4.3 Antimicrobial catheters

Different strategies are used to prevent catheter-associated nosocomial UTIs. One approach is the development of catheters coated with silver alloy or nitrofurazone (similar to nitrofurantoin) to prevent attachment by uropathogens. A meta-analysis of eight clinical trials since 1995 found that the use of these catheters reduced the risk of bacteriuria by up to 12% when compared to uncoated catheters (Johnson *et al*., 2006). Another strategy for long-term catheterization (e.g. patients with neurogenic bladder) is bacterial interference, where the bladder is deliberately colonized with an ABU *E. coli* isolate (ABU 83972) to prevent symptomatic infection. A randomized, double-blind placebo-control study found that over a period of one year, patients successfully colonized with ABU 83972 had an average 1.6 UTIs, whereas the placebo group experienced an average of 3.5 infections (Darouiche *et al*., 2005).

4.4 Immuno-stimulation

Polyvalent mixtures of killed uropathogens have been tested for their ability to prevent UTIs. UroVaxom (OM-89) is a lyophilized extract of 18 UPEC strains that is taken orally in Europe to prevent recurrent UTIs. It provides immunity to mice in experimental studies (Sedelmeier & Bessler, 1995). A meta-analysis of five placebo-controlled double-blind studies found that oral consumption of UroVaxom reduced the risk of UTI by 36% over 6 months (Naber *et al*., 2009). These findings were replicated in a large multicenter study (453 patients) that found a 34% reduction in UTIs over 1 year (Bauer *et al*., 2005). A related product is SolcoUrovac, a vaginal suppository containing lyophilized extract from six UPEC strains and one strain each of *P. mirabilis*, *Morganella morganii*, *K. pneumoniae* and *E. faecalis.* A Phase II randomized, double-blind placebo-control trial of 75 women with recurrent UTIs over 160 days observed a recurrence rate of 70% for the placebo arm and 27.5% for the vaccination plus booster arm of the study (Hopkins *et al*., 2007). Although these products appear useful to prevent recurrent UTIs, they are not vaccines *per se* as they require frequent administration. The clinical trial for UroVaxom had patients take one pill daily for 3 months,

no treatment for the next 3 months, then one pill daily for the first 10 days of each of the next 3 months followed by another 3 month cessation (Bauer et al., 2005). Similarly, the SolcoUrovac trial gave patients one suppository each week for the first three weeks, followed by an additional suppository each month for 3 months (Hopkins et al., 2007). Therefore, these treatments fall under the category of immuno-stimulation, rather than vaccination.

4.5 Vaccine development

Development of a UTI vaccine has also been a major research area. Vaccination of cynomolgus monkeys with type 1 fimbrial components protected them from UTIs (Langermann *et al*., 2000), as did vaginal immunization with formalin-killed UPEC (Uehling *et al.*, 1987). Vaccination of baboons and cynomolgus monkeys with another UPEC adhesin, purified P fimbriae, or components thereof, protected them from pyelonephritis (Roberts *et al*., 1989, Roberts *et al*., 2004). Immuno-correlates for successful vaccination appear to be antigen-specific serum IgG, as well as vaginal and urinary antibodies (Hilbert, 2011). Although these experimental studies of UPEC vaccination are promising, none of these candidates has progressed to clinical testing in humans.

5. Conclusion

In summary, rising antibiotic resistance among uropathogens, and especially the emergence of multi-drug resistant clonal groups, has provided urgency to the development of novel preventative and therapeutic strategies. Some older drugs, such as fosfomycin, may prove to be very useful in treating antimicrobial-refractory UTIs, especially those due to ESBL-producers. Newer drugs, such as the recently approved doripenem, have proven highly effective in the clinic to treat complicated UTIs. Research into novel anti-virulence therapies, such as inhibiting the production of, or adherence by, UPEC fimbriae is still an early stage but holds promise for future development. The use of probiotics to prevent vaginal UPEC colonization and the use of an immuno-stimulatory uropathogen extract (SolcoUrovac), are currently in clinical trials to determine efficacy in preventing recurrent UTIs. Another preventative strategy is vaccination, and experimental vaccines have been developed that are effective in preventing UTIs in primates. In summary, a combination of traditional and innovative prevention and treatment strategies is being deployed to combat the threat of emerging antibiotic resistance among uropathogens.

6. References

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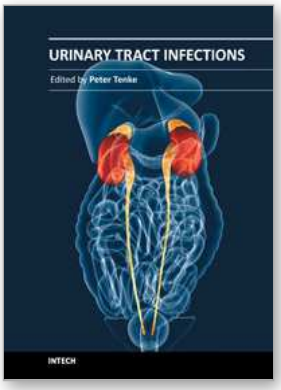

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Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, and they are also the leading cause of hospital-acquired infections. Therefore, the appropriate management of UTIs is a major medical and financial issue. This book covers different clinical manifestations of UTI, with special emphasis on some hard-to-treat diseases, and special conditions in respect of treatment; antibiotic resistance and the available alternative strategies for the prevention and treatment of UTIs and it deals with urinary tract infections in children. The aim of this book is to give a summary about the different aspects of the diagnosis, management and prevention of urinary tract infections for all medical disciplines.

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