INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Urinary Tract Infections*
-October 2021-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a therapeutic review of the treatment of urinary tract infections (UTI). Urinary tract infections are estimated to affect over 150 million people worldwide each year and are estimated to cost $3.5 billion in treatment and time from work[1]. Risk factors for UTI vary based on age. Pediatric risk factors include age, female sex, circumcision status, genetics, urinary obstruction (anatomic, functional, or neurologic), bladder or bowel dysfunction, vesicoureteral reflux, sexual activity, and bladder catheterization[2]. In adults, risk factors include female sex, active sexual intercourse, history of UTI, use of spermicide containing contraceptives, diabetes mellitus, and any structural or functional abnormality of the urinary tract[3]. This review evaluated current standards of care from the European Association of Urology (EAU), American Urologic Association (AUA), Infectious Disease Society of America (IDSA) and National Institute for Health and Care Excellence (NICE) guidelines and primary data evaluating antimicrobial and non-antimicrobial therapy for the treatment and prevention of UTI. Following clinical review and analysis, the NPTC voted to **ADD nitrofurantoin to the National Core Formulary.**

Discussion:

UTI therapy requires confirmation that the urinary tract is the source of infection, then determination of probable anatomic location and organism to be treated. Acute uncomplicated cystitis is defined as a bacterial infection isolated to the bladder. Acute complicated UTI encompasses many disease states such as pyelonephritis (upper UTI with systemic symptoms of bacterial infection such as fever, flank pain, and malaise), catheter associated UTI (UTI in the setting of urinary catheterization), UTI in men, and 'urosepsis' (sepsis from a urinary source). Other UTI classifications include asymptomatic bacteriuria (isolation of bacteria from a correctly collected urine specimen in the absence of UTI symptoms) and recurrent UTI (two separate culture proven episodes of acute bacterial cystitis and associated symptoms within six months or three episodes within one year). While evaluation of urinalysis is outside the scope of this review it is central to the diagnosis of UTI and clinicians should routinely review diagnostic criteria for the various populations they may treat.

Causative pathogens are an important consideration when choosing UTI therapy. *Escherichia coli* (*E.coli*) is the most common pathogen in UTIs among all ages and comorbidities. Other gram negative rods (GNRs) including *Klebsiella pneumonia, Proteus mirabilis, Enterobacter sp.*, and *Citrobacter sp*. should be considered as well as gram positives (GPBs) including *Staphylococcus saprophyticus*, *Enterococcus sp.*, and *Staphylococcus aureus*. Pathogens causing complicated UTIs can include any of the above as well as *Pseudomonas aeruginosa, Enterococci sp*., and multi-drug resistant organisms (MDRO). A study in 2016 reported up to 6% of all E. coli causing pyelonephritis were fluoroquinolone resistant[5]. Extended spectrum beta-lactamase (ESBL) resistance should be considered in high risk patients. In 2012 a sample of 5739 isolates from 72 US hospitals, the frequency of ESBLs was 16% in *K. pneumoniae*, 11.9% in *E. coli*, 10% in *K. oxytoca*, and 4.8% *in P. mirabilis*[4]. Risk factors for MDRO UTIs include history of MDRO infection, inpatient stay at a health care facility, use of a fluoroquinolone, trimethoprim-sulfamethoxazole (TMP-SMX), or broad spectrum beta-lactamase (3rd generation cephalosporin or greater), and travel to parts of the world with high rates of MDROs[6].

Society guidelines reviewed (EAU, IDSA, and NICE) did not have consensus with regards to therapeutics, often as a result of differences in available antimicrobials (e.g. pivecillinam, a first line therapeutic for acute bacterial cystitis, is not available in the United States). However important similarities led the NPTC to review a select group of antimicrobials: nitrofurantoin, fosfomycin, and fluoroquinolones. Nitrofurantoin is recommended by all three societies as first line treatment for acute uncomplicated cystitis, but is not recommended for complicated UTI or pyelonephritis. It demonstrated good in vitro activity against common pathogens and is an appropriate first-line agent for acute simple cystitis when no clear risk factors for resistance are present[3,6,8,9]. Fosfomycin is also recommended as first line for treatment of acute uncomplicated cystitis by EAU and ISDA and second line by NICE[3,8,9]. Use of fosfomycin is not recommended by any society for complicated UTI management [3,6,9]. Fluoroquinolones are the only antimicrobial class recommended across all three guidelines for empiric treatment of all categories of pyelonephritis[3,8,10].

Nitrofurantoin is a bactericidal agent that is well absorbed in its various forms (80% bioavailability) and excreted primarily in the urine[11]. It carries warnings for geriatric patients on the Beers List as well as the Pharmacy Quality Alliance against use in patients 65 and older particularly for long term therapy[11]. Other considerations for medication safety include potential for hemolytic anemia in patients with G6PD deficiency, cautious use in hepatic impairment, and cautious use in renal impairment, although there is data that supports short term use in patients with creatinine clearance (CrCl) 30-60 mL/minute[11]. Drug induced liver, lung and nerve toxicity are documented and often duration dependent[11]. Data for efficacy in acute uncomplicated cystitis in the 100mg twice daily for 5-7 days is excellent with clinical and microbiologic efficacy (resolution of clinical and microbiologic evidence of infection) of 93% and 88% respectively[3]. Susceptibilities of E. coli and most GNRs and GPBs have retained sensitivity despite widespread use, with the exception of *Klebsiella, Pseudomonas,*

Proteus, and *Morganella* which have intrinsic resistance[12]. A study examining microbial resistance to three, four or five antimicrobial agents demonstrated nitrofurantoin resistance was observed in 2.1%, 7.5% and 24.1% of isolates respectively while widespread resistance was observed for TMP-SMX (62.6%, 88.6% and 97.9%) and ciprofloxacin (48.9%, 84.3% and 98.2%)[14].

Fosfomycin is a bactericidal agent excreted into the urine as unchanged drug at high concentrations[13]. Fosfomycin is unique in its single-dose 3g sachet that is dissolved in cold water and taken orally[17]. Common adverse effects of fosfomycin include headache, diarrhea, nausea, abdominal pain, and dyspepsia[17]. Fosfomycin is active against *E. coli* with low minimum inhibitory concentrations. *Klebsiella, Proteus, Citrobacter, Enterobacter, Pseudomonas* and *Enterococcus* have variable susceptibility while *Morganella morganii* and *Acinetobacter* are typically resistant[13]. A 2013 study of antibiotic susceptibility of ESBL *E. Coli* demonstrated that nitrofurantoin and fosfomycin had the greatest activity against *E coli* (92% and 91% susceptibility respectively) and that *E faecalis* had 100% susceptibility to fosfomycin[16]. Compared head to head, nitrofurantoin (dosed 100mg thrice daily) resulted in a significantly increased likelihood of clinical and microbiologic resolution 28 days after treatment when compared to fosfomycin (dosed 3g once) (74% vs. 63% respectively, difference, 11% [95% CI: 1%-20%]; p=0.04)[15]. Although the study should be interpreted with caution as only 81% of participants had a positive urine culture. Adverse event rates were similar between the two medications[15].

While fluoroquinolones have remained a staple in treatment, they are fraught with concerns regarding safety. The drug class has excellent bioavailability (99%) and extensive tissue distribution[18]. All fluoroquinolones carry a black box warning for possible irreversible serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, and CNS effects[18]. Fluoroquinolones must also be avoided in patients with myasthenia gravis due to exacerbations of muscle weakness[18]. High rates of dysglycemia have been observed with many fluoroquinolones, including moxifloxacin, levofloxacin, and ciprofloxacin when compared with macrolides (OR of 2.13 [95% CI: 1.44-3.14], 1.79 [95% CI: 1.33-2.42], and 1.46 [95% CI 1.07-2.0], respectively; p<0.05)[19]. The FDA does recommend against prescription of fluoroquinolones to patients with or at risk for an aortic aneurysm. Several studies have demonstrated increased risk of aortic aneurysm or dissection, one retrospective cohort study conferred an HR of 2.24 (95% CI: 2.02-2.49) within 30 days of treatment[19].

The AUA recommends using antibiotics as prophylaxis to decrease the risk of recurrent UTI (rUTI) after shared decision making with consideration of risks and benefits with the patient[20]. Antibiotics for rUTI were associated with a decreased likelihood of experiencing ≥1 recurrence vs. placebo or no antibiotics (11 studies, RR 0.26, 95% CI: 0.18-0.37) and with increased risk of any adverse event (6 studies, RR 1.73, 95% CI: 1.08-2.79)[20]. Once antibiotics were stopped, UTIs recurred and equaled placebo arm outcomes[20]. Recommended antibiotics for rUTI prevention are nitrofurantoin 50mg-100mg once daily, TMP-SMX 40mg/200mg daily or thrice weekly, cephalexin 125mg-250mg daily, or fosfomycin 3g every 7-10 days with meta-analysis data demonstrating no singular antibiotic with superiority[20,21]. Non-antimicrobial treatments for rUTI such as topical estrogens, cranberry products, probiotics, D-mannose, and methenamine hippurate were also reviewed. Topical estrogens are recommended by the AUA for prevention of rUTI in peri- and post-menopausal women with supporting data demonstrating that vaginal estrogens (any formulation) are a potentially valid intervention[20,22]. Cranberry products are conditionally recommended by the AUA (grade C evidence) however a 2014 Cochrane Review comparing cranberry products with placebo found no benefit for most populations and a small benefit in some subgroups[20,23]. The AUA does not recommend probiotics due to lack of benefit, confirmed with a 2015 Cochrane Review which found no evidence for benefit compared with placebo[20,24]. Support for D-mannose use in rUTI prevention was demonstrated by a meta-analysis of 8 RCTs showing a low incidence of side effects and a pooled RR of rUTI with D-mannose vs. placebo of 0.23 (95% CI: 0.14–0.37) and pooled RR of rUTI with D-mannose versus preventative antibiotics of 0.39 (95% CI: 0.12–1.25) favoring D-mannose in both analyses[25]. The AUA does not recommend D-mannose in a review of 2 primary studies[20]. Methenamine hippurate is also not recommended by the AUA, however data from a Cochrane review revealed that short-term treatment duration (1 week or less) conferred a significant reduction in symptomatic UTI in those without renal tract abnormalities (RR 0.14, 95% CI: 0.05 to 0.38). A recent RCT comparing TMP-SMX and methenamine in prevention of rUTI with 65% (28 out of 43) recurrence in the antibiotic group versus 65% (28 out of 43) in the methenamine group (p=1.00) with similar rates of adverse events[20,26,27]. Perhaps evolving evidence on non-antimicrobial therapies will influence guidelines in the future.

Findings:

This review of UTIs revealed that treatment is variable depending on patient and clinical situation. Three notable therapies for treatment were nitrofurantoin, fosfomycin and fluoroquinolones. Both nitrofurantoin and fosfomycin are recommended as first line by most urologic societies for treatment of cystitis and both appear to have efficacy in resistant organisms with nitrofurantoin being slightly superior. Fluoroquinolones are a staple of pyelonephritis treatment but carry significant risks which must be considered given patient risk factors. Antibiotics for treatment and prophylaxis of recurrent UTI has excellent data for efficacy but high rates of adverse events. Other therapies such as cranberry products, D-mannose and methenamine hippurate have variable recommendations and data for use. Due to the presence of nitrofurantoin on many national guidelines, safety and efficacy for treatment and prevention of cystitis, nitrofurantoin was added to the National Core Formulary.

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