INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Male Genitourinary Infections*
-November 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed medications used to treat male genitourinary Infections at the November 2022 NPTC meeting. This was the first review of this condition for the Committee. As a result of this clinical evaluation, the NPTC **added (1) oral ciprofloxacin, (2) topical clotrimazole and (3) oral fluconazole** to the National Core Formulary.

Discussion:

Male genitourinary (GU) infections include balanitis, urethritis, epididymitis, prostatitis, cystitis, and pyelonephritis. Male GU infections are typically either sexually transmitted infections or caused by enteric pathogens. This distinction is important as it differentiates appropriate, empiric treatment. Sexually transmitted GU infectious pathogens typically include *Neisseria gonorrhea*, *Chlamydia trachomatis*, and *Mycoplasma genitalium*. Enteric pathogens which commonly cause GU infections are most often *Escherichia coli*, but can also be *Klebsiella pneumonia*, other gram-negative pathogens, and other, more rare pathogens (e.g., anaerobes or gram positives). Sexually transmitted infections (STI) have recently been reviewed extensively by the NPTC. As such, the primary focus of this brief is on non-STI pathogens and GU infections.[1,2]

The Agency for Healthcare Research and Quality (AHRQ) offers guidance for treatment of skin and soft tissue infections (SSTI). The AHRQ states that there are 4 moments in antibiotic decision making for SSTI; 1) determining if antibiotics are needed, 2) deciding whether cultures are needed and determining appropriate empiric therapy, 3) narrowing (IV to PO) or stopping antibiotics, and 4) appropriate antibiotic duration. Similarly, Goebel et al. suggests the 5 D's of antibiotic stewardship for urinary tract infections, including right diagnosis, right drug, right dose, right duration, and de-escalation.[1,3]

The first step in determining an appropriate treatment regimen is correctly determining the diagnosis. Different conditions, which are non-infectious in nature, can mimic GU infections. Other etiologies for delirium should be ruled out before antibiotic treatment is initiated in an otherwise asymptomatic elderly patient. Only after non-infectious causes have been ruled out, efforts should be made to determine whether the infection is an STI or not. Medication regimens, to include drug dose and duration, differ significantly between STI and other GU infections. In general, STI infections are more common in males <35 years old, and less common in males ≥35 years old. After attempting to rule out STI via sexual history and screening tests, if the clinician is unable to determine whether an infection is an STI or not, utilization of both empiric treatment options of STI and non-STI infections can be initiated until further lab tests and analysis is completed. Tests to rule out STIs, such as urine nucleic acid amplification test (NAAT), urine analysis, urine cultures (and blood in the case of pyelonephritis) should be initiated to determine effectiveness of therapy and guide de-escalation efforts. Cultures should not be drawn if patient is asymptomatic as it could lead to discovering asymptomatic bacteriuria. [1,4,5]

In males, there is no benefit to treat asymptomatic bacteriuria except in males undergoing invasive urologic procedures. The following is not diagnostic of a urinary tract infection (UTI); cloudy urine, pyuria, foul-smelling urine, organism type and number, and systemic leukocytosis (other sources of infection should be investigated).[1,6]

Once the patient is appropriately diagnosed with a non-STI GU infection, double strength trimethoprim-sulfamethoxazole (TMP-SMX DS) or ciprofloxacin are often the drugs of choice based on antibiotic resistance rates. For many non-STI GU infections, TMP-SMX DS would not be considered the drug of choice if local *E. coli* resistance rates are greater than 20%. Ciprofloxacin should not be considered for empiric treatment if local *E. coli* resistance rates are greater than 10%. Unfortunately, due to overuse of both of these antibiotics, it is common for individual areas in the United States to have *E. coli* resistance rates higher than these thresholds. As a result, tertiary treatment options including fosfomycin, nitrofurantoin, and beta-lactams are needed to successfully treat these infections. It is important that local antibiograms utilize appropriate sensitivity panels so providers have the best information available for empiric treatment decisions. One area where local sensitivity panels can be misleading is in utilizing ampicillin-sulbactam as a surrogate for amoxicillin-clavulanate. In-vitro, *E. coli* may still demonstrate sensitivity to amoxicillin-clavulanate despite demonstrating resistance to ampicillin-sulbactam. Similarly, cephalothin has been shown to be a suboptimal 1st generation surrogate for cefazolin and cephalexin. In-vitro, *E. coli* may still demonstrate sensitivity to cefazolin and cephalexin despite demonstrating resistance to cephalothin. *E. coli* sensitivity panels for nitrofurantoin are reliable but nitrofurantoin is only effective/indicated in treating lower UTI. Similarly, fosfomycin is only indicated for treating lower UTIs but case studies have suggested that it may have benefit in off-label treatment of other infections. As with all antibiotics, overuse of fosfomycin would lead to increased resistance. Currently, tracking resistance rates of fosfomycin is difficult as fosfomycin sensitivities are not widely available in the United States.[1,2,7-10]

Other determining factors when selecting appropriate therapy for non-STI GU infections include drug interactions, pharmacokinetics, and Black Box warnings. All fluoroquinolones, including ciprofloxacin, have a Black Box warning for tendinopathy and tendon rupture, peripheral neuropathy, and CNS effects. This includes all patients but it is more pronounced in the elderly. Additionally, fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. TMP-SMX has multiple drug interactions through cytochrome p450 inhibition and interacts with other medications (e.g., ACE inhibitors, ARBs) which could result in increased serum potassium and serum creatinine.[11,12]

Duration of treatment is typically 7-14 days depending on the non-STI GU infection. Treatment duration should be the shortest course possible while still adequately treating the infection. Antibiotic treatment duration variability is especially pronounced with treatment of complicated or catheter-associated UTIs. One reason for this variability is the lack of a consensus definition of what constitutes a complicated UTI. In general, complicated UTIs involve other factors which cause a UTI to be more difficult to treat, requiring higher doses of antibiotics and/or longer treatment duration. These factors include catheterization, anatomic or structural abnormalities, obstruction, reflux, azotemia, immunosuppression, transplant, and uncontrolled diabetes. The European Association of Urology guidelines identify male sex as a complicating factor, suggesting 14 days of treatment is often necessary. However, studies show consistently that 7 days is sufficient for treatment of otherwise uncomplicated UTIs in males. Regimens including nitrofurantoin 100mg po BID and amoxicillin-clavulanate 875/125mg po BID are effective treatments in these cases.[1,2,7,13-16]

Common Oral Treatment Options for Male, Non-STI GU Infections*[2,4-7,10, 13-24]

Diagnosis	Drug	Dose	Duration	Comments
Balanitis	Clotrimazole (topical)	To affected area BID	7 days	More severe cases may require oral fluconazole
Epididymitis	TMP-SMX DS Ciprofloxacin	1 tab po BID 500mg po BID	10-14 days	
Prostatitis (Acute)	TMP-SMX DS Ciprofloxacin	1 tab po BID 500mg po BID	10-14 days minimum	Use antimicrobials with ability to penetrate the prostate
Prostatitis (Chronic)	TMP-SMX DS Ciprofloxacin	1 tab po BID 500mg po BID	1-3 months	Cultures should be available to guide initial therapy
Uncomplicated cystitis	Multiple options**	Standard dose**	7 days	Dose is higher than uncomplicated cystitis in females
Complicated cystitis	Multiple options**	Standard dose**	7-14 days	Macrobid can be used for lower urinary tract infections
Pyelonephritis	Multiple options**	Standard dose**	7-14 days	Treatment duration data is variable. In general duration is shortest with ciprofloxacin, then TMP-SMX, followed by beta-lactams

** Please refer to antibiotic guidelines (e.g. EAU Guidelines on Urological Infections, Sanford Antibiotic Guide) for further information.*
***TMP-SMX-DS 1 tab bid x 7 days (If local prevalence of resistance of E. coli to TMP/SMX is < 20%), ciprofloxacin 500 mg twice daily (if local prevalence of resistance is <10%), nitrofurantoin (Macrobid) 100mg bid, amoxicillin-clavulanate 875/125 mg bid, cephalexin 500 mg qid, cefdinir 300 mg bid, fosfomycin 3 gm every 3 days x 3 doses*

Findings:

Antibiotic treatment for male GU infections should be targeted to treat the most likely pathogens given the type and source of the infection. Antibiotics should be given for the shortest duration possible. Local treatment options should be guided by local resistance patterns. Given the increased resistance of *E. coli* to ciprofloxacin and TMP-SMX, it is important that individual sites ensure that lab-reported *E. coli* sensitivities/surrogates are as relevant as possible to prevent needless escalations in therapy. Cephalothin is a poor surrogate for cephalexin and cefazolin. Ampicillin-sulbactam should be evaluated whether or not it is a sufficient surrogate for amoxicillin-clavulanate *E. coli* sensitivities. The NPTC voted to add topical clotrimazole and oral fluconazole to the NCF as they are the drugs of choice for mild and moderate-to-severe candidal balanitis respectively. Oral ciprofloxacin was also added to the NCF as an additional primary empiric treatment option for many male genitourinary infections.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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