TREATMENT OF URINARY TRACT INFECTIONS

Chapter 14

Bacterial infections of the urinary tract are the most common cause of both community- and hospital-acquired infections.

In this chapter, the treatment of urinary tract infections (UTIs) will be covered in the following categories:

- Women with acute uncomplicated cystitis
- Women with recurrent cystitis
- Women with acute, uncomplicated pyelonephritis
- Adults and children with complicated urinary tract infections

BACTERIAL CAUSES OF URINARY TRACT INFECTIONS IN SOUTH AFRICA

Escherichia coli is the most common bacterial cause of community- (~ 72% of cases) and hospital-acquired (~ 51% of cases) urinary tract infections. Of concern is the number of cases of UTIs caused by *Klebsiella pneumoniae* (at least 9% in community-acquired and at least 17% in hospital-acquired urinary tract infections). Other bacteria individually represent < 10% of the bacterial causes of UTIs. These include enterococci, group B Streptococci, other Enterobacteriaceae and non-fermenting Gram-negative bacilli.

For community-acquired urinary tract infections due to *Escherichia coli*, 2016 susceptibility data is shown in the following table. The data reflects Ampath susceptibility data from outpatients with UTIs in the Western Cape, Gauteng and Kwazulu-Natal provinces.

ANTIBIOTIC	% SUSCEPTIBLE E.COLI ACROSS THREE PROVINCES
Ampicillin/amoxicillin	27–33%
Amoxicillin–clavulanic acid	63–70%
Cefuroxime	66–70%
Ceftriaxone	73–92%
Ciprofloxacin	61–79%
Cotrimoxazole	42–47%
Fosfomycin	84–98%
Nitrofurantoin	85–98%

As susceptibility data may differ from area to area within each province, local susceptibility profiles should be determined for uropathogens isolated. A complicated urinary tract infection, the clinical diagnosis of pyelonephritis or history of previous antibiotic use are indications for a urine culture. In the light of ever worsening resistance patterns amongst bacteria, it is still debated whether urine culture should be performed for uncomplicated urinary tract infections. A lack of culture data for these uncomplicated cases make it an increasingly difficult to obtain local susceptibility profiles and thus appropriate empiric antibiotic recommendations.

ANTIBIOTIC TREATMENT OF URINARY TRACT INFECTIONS

Various classification schemes have been used to subdivide UTIs: upper versus lower tract, complicated versus uncomplicated, symptomatic versus asymptomatic. It is often difficult to make decisions based solely on one classification. A generally reliable approach is to consider uncomplicated urinary tract infections as either a lower or upper tract infection occurring in a healthy, non–pregnant woman with a structurally and neurologically normal genitourinary tract. A complicated UTI is one occurring in a patient with an underlying condition that increases the risk of treatment failure.

ACUTE UNCOMPLICATED CYSTITIS IN WOMEN

GENERAL PRINCIPLES

- Considerations when selecting an antibiotic for acute cystitis include resistance rates, efficacy, risk of adverse effects, cost and drug availability. For example, adverse side-effects from fluoroquinolones include *C. difficile* diarrhoea and tendinopathy and the risks may outweigh the benefits when used for the treatment of uncomplicated urinary tract infections.
- Single dose therapy is less effective in eradicating initial bacteriuria than extended durations of treatment with cotrimoxazole, fluoroquinolones and β-lactams.
- Three days of therapy is clinically equivalent to long durations for cotrimoxazole, norfloxacin and ciprofloxacin.
- Single dose fosfomycin (Urizone®) has emerged as a candidate for single dose therapy in uncomplicated UTIs, although adequate large trials are lacking in respect of assessing eradication rates, which appears to be lower than conventional three day regimens of cotrimoxazole and ciprofloxacin. Fosfomycin should be avoided if there is suspicion of early pyelonephritis.
- Most of the β-lactams (including amoxicillin, amoxicillin-clavulanate and the cephalosporins) appear to be less effective than cotrimoxazole and the quinolones in eradicating initial bacteriuria, and may be associated with increased recurrences. This is probably due to rapid excretion of most of the β-lactams from urine.
- A five to seven day course of nitrofurantoin has a clinical efficacy rate of 90–95% based on randomised trials. Nitrofurantoin should be avoided if there is suspicion of early pyelonephritis or if the creatinine clearance is < 30 mL/minute. If nitrofurantoin is prescribed, alkalinising agents (potassium citrate) should not be taken concurrently.
- The new quinolones such as moxifloxacin should not be used to treat UTIs since they achieve much lower urinary levels than ciprofloxacin and levofloxacin.
- Antibiotic options and suggested treatment durations for acute uncomplicated cystitis are the same for any adult woman with acute uncomplicated cystitis, regardless of age.

TREATMENT OF ACUTE UNCOMPLICATED CYSTITIS IN WOMEN

Ampath susceptibility data clearly shows sufficiently high resistance rates not to recommend cotrimoxazole and fluoroquinolones as empiric first-line therapy. For uncomplicated cystitis one would expect that more than 90% of patients will achieve eradication of bacteriuria with a low risk of recurrence. Due to the high levels of resistance to cotrimoxazole and ciprofloxacin, we therefore strongly recommend that patients who are treated empirically with either agent, be monitored clinically for relapse and have urine samples submitted for culture should a relapse occur.

AMPATH'S RECOMMENDATIONS FOR ACUTE UNCOMPLICATED CYSTITIS

Nitrofurantoin 100 mg PO 12 hourly for 7 days

OR

Fosfomycin 3 g PO given as a single dose

Do not use nitrofurantoin or fosfomycin if there is any suspicion of early pyelonephritis as they do not achieve adequate renal tissue levels.

If there are any factors precluding the use of the above agents, then a beta-lactam should be used. Options include:

Cefixime 200 mg PO 12 hourly for 7 days

OR

Cefpodoxime 100 mg PO 12 hourly for 7 days

YOUNG WOMEN WITH RECURRENT CYSTITIS

Recurrent infection refers to ≥ two infections in six months or ≥ three infections in one year and occurs in roughly five to ten percent of women. Recurrent infection is a result of re-infection or a relapsing infection. A recurrence is defined clinically as a 'relapse' if it is caused by the same bacterial species which caused the original UTI, and if it occurs within two weeks after treatment was initiated. It is considered 're-infection' if it occurs more than two weeks after treatment of the original infection regardless of the bacterial strain isolated. Most women with recurrent UTIs have re-infections, whilst a minority are due to relapses. It is useful to distinguish clinically between relapse and re-infection, because relapsing infection requires urologic evaluation, longer therapy, and surgery in some cases.

PROPHYLAXIS AND TREATMENT OF RECURRENT CYSTITIS

Antimicrobial prophylaxis has been demonstrated to be highly effective in reducing the risk of recurrent UTIs in women. Continuous prophylaxis, post-coital prophylaxis, and intermittent self-treatment have all been demonstrated to be effective in the management of recurrent uncomplicated cystitis. Before any prophylaxis regimen is initiated, eradication of a previous UTI must be assured by obtaining a negative urine culture one to two weeks after treatment.

PROPHYLAXIS AND TREATMENT OF RECURRENT UNCOMPLICATED CYSTITIS IN WOMEN

POSTCOITAL PROPHYLAXIS

Nitrofurantoin 100 mg PO as a single dose

OR

Cephalexin 250 mg PO as a single dose

CONTINUOUS DAILY PROPHYLAXIS

Nitrofurantoin 100 mg PO once daily

OR

Cephalexin 250 mg PO once daily

Once daily prophylaxis can be given for 6 months, or for 2 years in women who continue to have symptomatic infections.

Long-term exposure to nitrofurantoin has been associated with pulmonary reactions, chronic hepatitis and neuropathy. These toxicities are rare but patients should be warned about them. In general, nitrofurantoin use should be avoided in patients with a creatinine clearance < 30 mL/minute in whom efficacy may be decreased and the risk for toxicity may be greater.

SELF-TREATMENT

Nitrofurantoin 100 mg PO 12 hourly for 7 days

OR

Fosfomycin 3 g PO as a single dose

OR

Cefixime 200 mg PO 12 hourly for 7 days

OR

Cefpodoxime 100 mg PO 12 hourly for 7 days

Women should be instructed to begin a course of an antibiotic (as above) at the onset of symptoms and to seek medical attention if symptoms do not resolve within 48–72 hours after completion of the course.

NOTE

Replacement topical oestrogen normalises the vaginal flora and greatly reduces the risk of UTIs in postmenopausal women. Intravaginal oestrogen is a reasonable option for postmenopausal women not taking oral oestrogen who have three or more recurrent UTIs per year, particularly when antimicrobial resistance to multiple drugs limits the efficacy of prophylaxis.

ACUTE UNCOMPLICATED PYELONEPHRITIS IN WOMEN

- Acute uncomplicated pyelonephritis is suggested by flank pain, nausea/vomiting, fever, and/or costovertebral angle tenderness.
- Urine culture and susceptibility testing should be performed in patients with known or suspected pyelonephritis, and initial empiric therapy should be tailored appropriately on the basis of the infecting pathogen.
- Oral antibiotics under supervision can be given on an outpatient basis to patients with mild to moderate illness once stabilised in hospital with rehydration and initial parenteral antibiotic therapy.
- Parenteral antibiotics and hospitalisation are generally recommended for pregnant women and patients with severe illness (vomiting and features of urosepsis).
- Fluoroquinolones are the only oral antimicrobials recommended for the empirical outpatient treatment of acute uncomplicated pyelonephritis. Due to the high rates of fluoroquinolone resistance, we would not recommend their use until the uropathogen isolated is shown to be susceptible.

TREATMENT OF PYELONEPHRITIS

Empiric intravenous therapy with such a long-acting, broad spectrum parenteral antimicrobial should be administered until susceptibility data are available. In all cases, subsequent therapy should be tailored based on susceptibility data. Parenteral therapy options include:

Ceftriaxone 1 g IV once daily

OR

Amikacin 15 mg/kg IV once daily

OR

Ertapenem 1 g IV once daily

De-escalate to narrower spectrum oral antibiotics after clinical response, and ideally with evidence of in-vitro susceptibility. Oral options include:

Ciprofloxacin 500 mg PO 12 hourly

OR

Levofloxacin 750 mg PO once daily

OR

Cefixime 200 mg PO 12 hourly

OR

Cefpodoxime 100 mg PO 12 hourly

OR

Amoxicillin-clavulanate 875/125 mg PO 12 hourly

OR

Cotrimoxazole 1 DS tablet (160/800) PO 12 hourly

Complete a total of 14 days of antibiotic therapy

If using ciprofloxacin or levofloxacin, a total of 7 days of treatment may be used for mild to moderate infections.

COMPLICATED URINARY TRACT INFECTIONS

This is defined as a UTI occurring in patients with underlying conditions that increase the risk of treatment failure. Such patients include:

- Those at the extremes of age – neonates, infants, children and the elderly
- Adult males
- Those with a foreign body (e.g. urethral catheter)
- Pregnant women
- Immunosuppressed patients (e.g. diabetes, malignancy, HIV)
- Those with an anatomic or functional abnormality (e.g. obstruction, neurogenic bladder, renal stones)
- Those infected with a resistant organism

The spectrum of uropathogens causing complicated UTIs is much broader than those causing uncomplicated UTIs. Common causes include *E. coli, P. mirabilis, Klebsiella* spp., *Serratia* spp, *Enterobacter* spp., *P. aeruginosa, A. baumanii*, staphylococci, *E. faecalis* and *Candida* species. These uropathogens are more likely to be resistant to the commonly-used antimicrobials. Therefore urine cultures must be obtained to identify the organism and obtain sensitivities to guide appropriate antimicrobial therapy. Where symptoms persist beyond 48 hours, blood cultures should be collected, and the urinary tract and abdomen should be imaged to exclude collections.

Patients with mild to moderate complicated UTIs can be treated as outpatients. Empiric oral cefixime or cefpodoxine are recommended. Parenteral antibiotics are recommended for more severe infections. Ceftriaxone and ertapenem are suitable empiric options (for doses refer to those used for uncomplicated pyelonephritis). Antibiotic therapy should be modified once the infecting organism is identified and susceptibilities are known.

The carbapenems, including meropenem and imipenem should ideally be reserved for patients with multidrug-resistant Gram-negative bacilli such as *P. aeruginosa* and extended-spectrum β-lactamase (ESBL) producing Enterobactericeae. *E. faecalis* requires treatment with ampicillin 1 g IV six hourly or amoxicillin 500 mg orally eight hourly.

Treat for seven to 14 days and repeat urine cultures after one to two weeks of completion of therapy.

URINARY TRACT INFECTIONS IN NEONATES

The signs and symptoms of UTIs in neonates are nonspecific. Infants may have lethargy, irritability, tachypnea or cyanosis and may appear acutely ill. A laboratory diagnosis is based on the culture of an organism from an appropriately collected specimen of urine, usually by suprapubic aspiration or urethral catheterisation. Approximately one third of newborns with UTIs have an accompanying bacteraemia and thus a set of blood cultures should be collected in all newborns in whom a UTI is suspected.

Newborns with UTIs should be evaluated with ultrasonography and a voiding cystourethrogram for anatomical or functional abnormalities of the urinary tract, including vesico-ureteric reflux, posterior urethral valves, ectopic ureters, polycystic kidneys and renal dysplasia.

Most UTIs in newborns and infants are caused by Gram-negative aerobic bacilli, with *E. coli* accounting for ~ 80% of infections. The other Enterobactericeae which cause UTIs in this group include *Klebsiella, Enterobacter, Citrobacter, Proteus, Providencia, Morganella* and *Serratia.* Fungal UTIs, predominantly caused by *Candida* spp., occur commonly in premature infants.

TREATMENT OF URINARY TRACT INFECTIONS IN NEONATES

Treat with empiric ampicillin 50 mg/kg per dose IV 8 hourly **AND** gentamicin 4 mg/kg IV once daily.

An alternative regimen (no *P. aeruginosa* and enteroccal cover) is:

Cefotaxime 150 mg/kg/day IV in 3 divided doses

OR

Ceftriaxone 50–75 mg/kg IV once daily

Empiric antibiotic therapy should be changed based upon the bacteria isolated and its antimicrobial susceptibility, and if there is a concurrent infection such as sepsis or meningitis. Duration of therapy is 10–14 days.

A follow up urine culture after 48 hours of completing antibiotic therapy is advised.

URINARY TRACT INFECTIONS IN INFANTS AND CHILDREN

Urinary tract infections are a common infection in childhood. Acute pyelonephritis may lead to renal scarring, hypertension and end-stage renal disease. Although children with pyelonephritis tend to present with fever, it is often difficult on clinical grounds to distinguish cystitis from pyelonephritis, particularly in children under two years of age.

Urine should be obtained by catheterisation or suprapubic aspiration for microscopy and culture in infants and young children who are not toilet-trained. A clean-voided specimen is the preferred method of collection in toilet-trained children. Children 12 months or older with a mild UTI (afebrile,

no nausea or vomiting) can be treated with oral antibiotics. Children 12 months or older who appear septic, and all infants < 12 months of age, should initially be treated with IV antibiotics.

TREATMENT OF URINARY TRACT INFECTIONS IN INFANTS AND CHILDREN

EMPIRIC ORAL ANTIBIOTICS FOR MILD INFECTIONS

Amoxicillin-clavulanate 25 to 45 mg/kg/day PO divided 12 hourly

OR

Cefixime 8 mg/kg/day PO divided 12 hourly

OR

Cefpodoxime 10 mg/kg/day PO divided 12 hourly

EMPIRIC IV ANTIBIOTICS FOR SEVERE INFECTIONS IN CHILDREN:

Treat with empiric ampicillin 50 mg/kg per dose IV 8 hourly **AND** gentamicin 4 mg/kg IV once daily

OR

Cefotaxime 150 mg/kg/day IV in 3–4 divided doses

OR

Ceftriaxone 50–75 mg/kg IV once daily

Parenteral antibiotics should be continued until the patient is clinically improved and able to tolerate oral liquids and medications. Empiric antibiotic therapy should be changed based upon the bacteria isolated and its antimicrobial susceptibility.

Treat for a total 5 days for cystitis or for 10–14 days for acute pyelonephritis.

URINARY TRACT INFECTIONS IN ADULT MEN

Symptomatic urinary tract infections are much less common in men than in women, and all UTIs in men are considered complicated UTIs. Men with UTIs should be evaluated for predisposing or causative factors. Laboratory urinalysis is required in all suspected cases and pyuria is present in almost all men with acute cystitis or pyelonephritis. The absence of pyuria suggests an alternative diagnosis, or in a patient with pyelonephritis the presence of an obstructing lesion.

Nitrofurantoin and beta-lactams are generally not used for men with cystitis, since they do not achieve reliable tissue concentrations and are less effective for occult prostatitis. Data for fosfomycin use in men is limited.

TREATMENT OF URINARY TRACT INFECTIONS IN ADULT MEN

EMPIRIC ORAL ANTIBIOTICS FOR CYSTITIS

Ciprofloxacin 500 mg PO 12 hourly

OR

Levofloxacin 750 mg PO once daily

Empiric antibiotic therapy should be changed based upon the bacteria isolated and its antimicrobial susceptibility.

Treat for a total of 7–14 days

EMPIRIC PARENTERAL ANTIBIOTICS FOR PYELONEPHRITIS

Intravenous therapy with a long-acting, broad spectrum parenteral antimicrobial should be administered until susceptibility data is available. In all cases, subsequent therapy should be tailored based on susceptibility data. Parenteral therapy options include:

Ceftriaxone 1 g IV once daily

OR

Amikacin 15 mg/kg IV once daily

OR

Ertapenem 1 g IV once daily

De-escalate to a narrower spectrum oral antibiotic after a clinical response, and ideally with evidence of in-vitro susceptibility.

Treat for 14 days (a 7–day course can be used for patients treated with a quinolone).

ACUTE AND CHRONIC PROSTATITIS

Refer to the chapter 'Genital tract infections'

CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

Urinary tract infections associated with urinary catheters are the leading cause of secondary health care-associated bacteraemia. Patients may present with fever and/or flank or suprapubic discomfort, costovertebral angle tenderness and catheter obstruction. Non-specific presentations include new onset delirium or other systemic manifestations that suggest the possibility of infection.

The causative pathogens in catheter-associated urinary tract infection and asymptomatic bacteriuria are similar to those that are associated with complicated cystitis in general, and include *Candida* spp. and *P. aeruginosa*. Only symptomatic patients with indwelling urinary catheters will require urine MC&S and antibiotic therapy (if culture positive). Treatment of asymptomatic bacteriuria in catheterised patients does not decrease the incidence of febrile episodes and is not routinely indicated.

If an indication to investigate a possible catheter-associated UTI exists, ideally the urinary catheter should be replaced and a urine culture be collected via the newly placed catheter. Whenever possible, antimicrobial selection should be based upon the culture and susceptibility results.

Candiduria is a common finding in patients with indwelling bladder catheters, particularly in those taking antibiotics. Most are asymptomatic, where the candiduria represents colonisation and hence antifungal treatment is not usually necessary.

If treatment is required prior to the culture results, the recommended empiric choices should be based on the most likely pathogens seen in a particular unit or hospital, prior antimicrobial therapy and previous urine culture results.

TREATMENT OF CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

Antimicrobial therapy of catheter-associated UTI is similar to that for acute complicated cystitis

EMPIRIC ORAL ANTIBIOTICS FOR THOSE NOT SEVERELY ILL

Cefixime 200 mg PO 12 hourly

OR

Cefpodoxime 100 mg PO 12 hourly

OR

Ciprofloxacin 500 mg PO 12 hourly

OR

Levofloxacin 750 mg PO once daily

EMPIRIC PARENTERAL ANTIBIOTICS FOR THOSE SEVERELY ILL WITH UROSEPSIS:

Cefotaxime 1 g IV 8 hourly

OR

Ceftriaxone 1 g IV once daily

OR

Ertapenem 1 g IV once daily

The presence of Gram-positive cocci on the Gram stain suggests a possible enterococcal UTI, for which ampicillin 1 g PO 6 hourly or amoxicillin 500 mg PO 8 hourly are the antibiotics of choice.

De-escalate to narrower spectrum oral antibiotics after a clinical response, and ideally with evidence of in-vitro susceptibility.

Treat for 7 days in patients in whom pyelonephritis is unlikely and not suspected, and for 10–14 days in whom pyelonephritis is suspected or diagnosed.

URINARY TRACT INFECTIONS IN PREGNANCY

Urinary tract infections are common in pregnant women and may increase the risk of adverse pregnancy outcomes such as preterm birth and unexplained perinatal death.

UTIs in pregnancy may present with:

- Asymptomatic bacteriuria
  - Usually develops in the first month or two of pregnancy
  - Screening for bacteriuria by urine culture (not dipstick screening) is recommended for all pregnant women at least once in early pregnancy typically at the first antenatal visit
  - If bacteriuria is left untreated it can progress to pyelonephritis in ~ 40% of pregnant women
- Acute cystitis – considered a complicated UTI in pregnancy
- Acute pyelonephritis – always considered a complicated UTI in pregnancy

TREATMENT OF URINARY TRACT INFECTIONS IN PREGNANCY

It is generally accepted that penicillins and cephalosporins are safe in pregnancy. Fosfomycin also appears to be safe in pregnancy. Nitrofurantoin is frequently used in pregnancy, although some safety concerns exist.

Trimethoprim (and therefore cotrimoxazole) should be avoided, especially in the first trimester. Quinolones and tetracyclines are contraindicated throughout pregnancy.

ASYMPTOMATIC BACTERIURIA IN PREGNANCY

Treat according to the laboratory susceptibility results and perform follow-up cultures to confirm sterilisation of the urine

EMPIRIC ANTIBIOTIC CHOICES FOR ACUTE CYSTITIS IN PREGNANCY:

Cefpodoxime 100 mg PO 12 hourly for 7 days

OR

Cefixime 200 mg PO 12 hourly for 7 days

OR

Amoxicillin-clavulanate 875/125 mg PO 12 hourly for 7 days

OR

Nitrofurantoin* 100 mg PO 12 hourly for 7 days

OR

Fosfomycin** 3 g PO as a single dose

Empiric antibiotic therapy should be changed based upon the bacteria isolated and its antimicrobial susceptibility.

* Nitrofurantoin is contraindicated near term as it may cause neonatal haemolytic anaemia

** Safety of fosfomycin in pregnancy has not been definitively established

ACUTE PYELONEPHRITIS IN PREGNANCY

Acute pyelonephritis is traditionally treated by hospitalisation with IV antibiotics until the woman is afebrile for 24 hours and symptomatically improved. Once afebrile for 48 hours, the patient can be switched to oral antibiotics based on culture susceptibility results and discharged to complete a 14 day course of treatment. Recommended initial empiric IV antibiotic are:
Cefotaxime 1 g IV 8 hourly
OR
Ceftriaxone 1 g IV once daily