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REVIEW

Urinary tract infections in children

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Abstract

Urinary tract infections (UTIs) are common in childhood and represent approximately 10% of hospital-acquired infections. It is clinically challenging to distinguish cystitis (lower UTI) from pyelonephritis (upper UTI) in those younger than two years. Most UTI patients can however be safely managed as outpatients if diligent follow-up procedures are in place. Recurrent UTIs in children may indicate malfunction or an anatomical defect of the urinary tract, and require specialised diagnostic studies. The proper approach for a child with UTI remains controversial, and treatment often differs according to regional or institutional empirical guidelines.

Keywords: Urinary tract infection, children, cystitis, pyelonephritis, antibiotics

Introduction

Urinary tract infections (UTIs) are common febrile infections in paediatric practice with 8% of girls and 2% of boys having at least one episode by 7 years of age.[1,2] UTIs in children account for 5–14% of emergency department visits by children annually. The prevalence among infants is 7%.[3,4] During the first few months of life, the incidence of UTIs in boys exceeds that in girls, however these infections are more common in females after the first year. Uncircumcised male infants less than 3 months of age have a higher prevalence of UTIs compared to their circumcised counterparts (2.4% vs 20.1%), while non-febrile UTIs are more frequent in girls older than 3 years of age.[5,6,7,8]

The uncomplicated UTI is limited to the lower urinary tract (cystitis or urethritis) with no urological anomalies and mostly affects girls over the age of 2 years. Complicated UTIs involve the renal parenchyma (pyelonephritis), and are usually associated with underlying congenital anomalies of the kidneys and urinary tract.[9] These UTIs may result in significant short-term morbidity, including septicaemia and acute renal failure, especially in infants. Renal parenchymal defects are present in 3–15% of children within 1–2 years following their first diagnosed UTI. Nearly 10–15% of children with one febrile UTI or pyelonephritis develop renal scarring.[10,11] This risk is significantly increased in the presence of recurrent UTIs and associated urological abnormalities. Therefore, all febrile infants or children under the age of 2 years presenting with pyrexia of unknown origin, should be evaluated for the presence of a UTI.[12]

The American Academy of Pediatrics (AAP) criteria for the diagnosis of UTIs in children 2–24 months include the presence of pyuria and/or bacteriuria on urinalysis, and the presence of at least 50,000 colony-forming units (CFU) per ml of a uropathogen collected from an acceptable urine specimen. In neonates younger than 2 months, criteria include the presence of lower amounts of a single pathogen (10,000–50,000 CFU/ml).[6,7] According to the South African Standard Treatment Guidelines and Essential Medicines List for Hospital Level (2013), diagnosis depends on the presence of any culture from a suprapubic urine sample, or a culture of more than 10,000 CFU/ml urine of a single organism from a catheter specimen, or a pure culture of > 100,000 CFU/ml in a mid-stream clean catch sample, or consistent culture of a pure growth even with counts as low as 10,000 CFU/ml.

In most patients, the presence of pyuria should be considered in conjunction with colony counts to establish the clinical significance of culture results, and to reduce the possibility of a false-positive diagnosis. The presence of significant pyuria may be particularly valuable in distinguishing asymptomatic bacteriuria from sample contamination during collection. Susceptibility to UTI may be increased in patients with bowel and bladder dysfunction, alteration of the periurethral flora following antibiotic therapy, or neurogenic and anatomic abnormalities of the urinary tract. Renal and bladder ultrasonography are indicated in all children younger than 2 years presenting with a first episode of febrile UTI lasting longer than 24 hours. Imaging studies should also be considered in children of any age with recurrent febrile UTIs, a family history of urological disease and those who do not respond to appropriate antimicrobial therapy. Voiding cystourethrography (VCUG) is recommended when ultrasonography reveals hydronephrosis, scarring, obstructive

uropathy or other underlying anatomic disorders requiring surgical correction. Approximately 25–30% of children with two or more febrile UTIs will have vesicoureteral reflux diagnosed by VCUG.[13,14,15]

The most common cause of UTIs in all age groups is *Escherichia coli* (up to 85%). Other gram negative organisms include *Klebsiella* (23%), *Proteus* (7%), *Citrobacter, Enterobacter* and *Pseudomonas aeruginosa*. Gram-positive bacterial pathogens include *Enterococcus* species (patients with a urinary catheter in place, instrumentation of the urinary tract, or an anatomical abnormality), *Staphylococcus saprophyticus* (up to 4%), which is predominant in sexually active adolescents and *Streptococcus* group B that is common among neonates. Viruses and fungi are rarely responsible for UTIs in children, with the exception of *Candida* species in preterm neonates. Multiple organisms may be present in patients with structural abnormalities.[16,17,18]

Diagnosis

An accurate, reliable diagnosis of UTIs in children is essential, especially in those below the age of 2 years where the clinical presentation may be nonspecific. Neonates and infants younger than 2 months having pyelonephritis often lack symptoms localised to the urinary tract. UTI is mostly discovered as part of an evaluation for neonatal sepsis. Neonates may present with jaundice, fever, failure to thrive and poor feeding, vomiting and irritability. Infants and children from age 2 months to 2 years may present with fever, vomiting, abdominal pain, foul-smelling urine, poor feeding and irritability. Children older than 2 years may additionally present with enuresis, dysuria, urgency, frequency and flank/back pain. Physical examination often reveals costovertebral angle, abdominal and suprapubic tenderness.[17,19,20]

Urine specimen collection requires a precise method to avoid false positive results. A midstream, clean-catch specimen is obtained from children who have urinary control. Febrile infants, children with sepsis, and all children who have an urgent clinical indication to start antibiotics, and are unable to void necessitate catherization. Contraindications to urinary catherization include gross infection of the genital area, labial adhesions in females, or failure to visualize the urethral opening in uncircumcised males. Suprapubic urine aspiration is considered for uncircumcised boys with a redundant or tight foreskin, girls with tight labial adhesions and all children with clinically significant periurethral irritation, including those who cannot be catheterized or are unable to produce an uncontaminated midstream sample.[21] Culture of a urine specimen from a sterile bag applied over the vulva or penis and scrotum is not suitable for accurate diagnosis due to the high rate of the false-positive results, however, a negative culture is strong evidence that UTI is absent.[22]

Urine dipstick testing may be used as an initial screening method for UTIs, however urinalysis alone is not sufficient for diagnosing UTIs in children. A UTI is likely with a positive dipstick indicating leukocyte esterase and nitrites, or with pyuria of at least 10 white blood cells per high-power field (on a suprapubic aspirate, the presence of 5 or more WBCs per high-power field).[23] Although possible, pyuria is uncommon in the absence of true UTIs. Negative dipstick nitrate readings, including the absence of bacteria under direct microscopy is commonly seen in children, which often results in the failure to exclude a UTI. The urinary nitrite test requires approximately four hours for an uropathogen to convert dietary nitrates into nitrites in the bladder responsible for a positive test. With the rapid physiological bladder emptying present in infants and children, especially those with inflammation associated with UTIs, this test may be falsely negative. Other causes of false-negative reactions include uropathogens lacking the mechanism to reduce nitrates to nitrites (*Enterococcus* spp., *Staphylococcus saprophyticus*, *Pseudomonas aeruginosa*, and *Candida* spp.), bacteriostatic antimicrobial agents (macrolides, sulphonamides), and obstruction of the ureter interfering with the discharge of bacteria into the bladder.[24] Thus, evaluating urinary nitrites as a single test has a high specificity (98%), but much lower sensitivity (49%) for detecting UTIs in children.[25] Children with unexplained fever or voiding symptoms may have positive urinary cultures even when abnormal findings are not evident on dipstick testing and complete urinalysis. Approximately 10–20% of pediatric patients with UTIs have normal urinalysis results.[26] Laboratory studies including complete blood count (CBC) and basic metabolic panel (for children with a presumptive diagnosis of pyelonephritis), blood cultures (in patients with suspected bacteremia or sepsis), renal function studies (i.e., serum creatinine and blood urea nitrogen levels) and electrolyte levels should be done additionally.[27] Determining the procalcitonin level may prove helpful in diagnosing pyelonephritis.[28]

Pharmacological management

The successful management of an acute UTI requires the initiation of aggressive empirical antibiotic therapy after urine has been collected, but prior to culture and antimicrobial susceptibility results are available. Empirical treatment is started within 72 hours of presentation to prevent renal damage such as scarring, cysts, hypertension and end-stage renal dysfunction. Decisions regarding initiation of empirical treatment depends on various factors. These include the most likely causative organism, community resistance patterns, age of the child, underlying medical or urological conditions, severity of infection, and recent antibiotic exposure.[29] Approximately 50% of *E. coli* are resistant to amoxicillin or ampicillin.[30] Resistance to first-generation cephalosporins (cephalexin), amoxicillin-clavulanate and trimethoprim-sulfamethoxazole combinations is also on the increase.[31,32,33] Risk factors for resistance include lack of circumcision in boys, bowel and bladder dysfunction, and recent antibiotic exposure.[30]

Most children older than 2 months who are not vomiting, can be treated with oral therapy. Parenteral antibiotics are recommended for infants with febrile UTIs, presence of sepsis, patients with immune-compromising conditions, and those with an inability to take oral medication.[34,35] Currently there is no consensus regarding the duration of treatment. A recent systematic review found short-course antimicrobial therapy (2–4 days) to be equally effective as standard duration (7–14 days) treatment. It is suggested to use a longer course

Table 1. Antibiotics used to treat UTIs in children

Active Ingredient	Dose	Side effects	Comments
		Penicillins	
Amoxicillin/ clavulanic acid	Dose according to amoxicillin component Neonates and less than 12 weeks • 15 mg/kg/dose 12 hourly orally Children 3 months and older (Less severe infections) • 10–15 mg/kg/dose 8 hourly OR • 15–25 mg/kg/dose 12 hourly Children 3 months and older (more severe infections) • 30–40 mg/kg/dose 8 hourly OR • 45 mg/kg/dose 12 hourly Severe infections: • IV, 50–100 mg/kg daily, given in divided doses	Common • Gastrointestinal disturbances (diarrhea nausea/vomiting) • Mucocutaneous candidiasis • Maculopapular rash Uncommon • Dizziness, headache • Hepatitis and cholestatic jaundice (occurring up to 6 weeks after therapy) • Fatal hypersensitivity reactions	• Gastrointestinal disturbances largely attributed to clavulanic acid • Side effects may be minimised by taking with meals • When using the higher dosage add amoxicillin separately to limit the clavulanic acid side effects • Rather avoid if GFR < 30ml/min
Ampicillin	Neonates • 50 mg/kg/dose 12 hourly in the first week of life, 8 hourly thereafter Children under 20 kg • 10–25 mg/kg/dose 6 hourly Children over 20kg • 30–40 mg 6 hourly	• As for penicillins	• Used for initial treatment of patients with acute pyelonephritis due to Gram-positive cocci and patients allergic to cephalosporins • Used with gentamicin in neonates < 2 weeks of age
		Cephalosporins	
Cephalexin (1st generation)	• 25–50 mg/kg/day in divided doses • Maximum 100 mg/kg/day or 4 g/day	• Cross-sensitivity may occur for all cephalosporin in patients allergic to penicillin • Diarrhea, headache, nausea/ vomiting, rash, abdominal pain • Elevated liver enzymes • Neurotoxicity, nephrotoxicity • Steven Johnson syndrome occurs rarely	• Widespread resistance in Gram-negative species
Cefprozil (2nd generation)	• Oral 15 mg/kg/dose 12–24 hourly • Maximum 500 mg		• Effective against beta-lactamase-producing *H.influenzae, E.coli, B.fragilis, Klebsiella and Proteus* species • *Pseudomonas* and *Acinetobacter* species are not susceptible
Cefuroxime (2nd generation)	Neonates • IM or IV, 25–50 mg/kg/dose, 12 hourly in the first week of life, then 6–8 hourly Children 1 month and older • Oral, 10–15 mg/kg/dose (maximum 250 mg) 12 hourly		• Not effective against *Bacteroides* or *Proteus* species.
Cefoxitin (2nd generation)	• IM or IV, 25–60 mg/kg/dose (maximum 3g) 6–8 hourly; Dose 12 hourly in the first week of life		• As for cefuroxime
Cefixime (3rd generation)	• 8 mg per kg every 24 hours or divided every 12 hours		• Good activity against most Gram-positive and Gram-negative organisms
Cefpodoxime (3rd generation)	• 5–8 mg/kg/dose 12 hourly		
Cefotaxime (3rd generation)	Neonates • 50 mg/kg/day IV/IM divided q6–8h in the first week of life, from 1–3 weeks 6 hourly Children 1 month and older • 25 mg/kg/dose IV/IM 6 hourly • Severe infection: 50 mg/kg/dose 6 hourly		• Safe to use in infants < 6 weeks of age • May be used with ampicillin in infants aged 2–8 weeks
Ceftriaxone (3rd generation)	• IM or slow IV, 50–75 mg/kg/daily given in a single dose of 2 divided doses (maximum 2 g per dose) • Doses exceeding 50 mg/kg by IV infusion only		• Effective against Gram-positive and Gram-negative penicillin resistant organisms, including *Enterobacteriaceae, H. influenza, N. meningitides, S. pneumonia,* and *N. gonorrhoeae.* • Ineffective against *P. aeruginosa and enterococci* • Limited anaerobic cover • In renal impairment, no dosage adjustment is required if creatinine clearance > 5 ml/min provided that hepatic function is normal. • In hepatic disease, dosage reduction (50%) is only required in cirrhosis when serum albumin levels are low. • Not to be used in infants < 6 weeks as it may displace bilirubin from albumin

Cefepime (4th generation)	• 25 mg/kg/dose IV or IMI 12 hourly • Severe infection: 50 mg/kg/dose 8–12 hourly (maximum dose of 2 g)	• Non-convulsive status epilepticus reported in patients with renal impairment	• Active against Gram-positive and Gram-negative infections, including resistant *P.aeruginosa, S. aureus* and *S. pneumoniae*
Aminoglycosides			
Gentamicin	Neonates • 6 mg/kg/day IV or IMI 12 hourly Children 1 week – 10 years: • 8 mg/kg/day for first day then 6 mg/kg/day Children 10 years and older • 7 mg/kg/day for 1 day then 5 mg/kg/day	• Irreversible ototoxicity • Nephrotoxicity • Blood dyscrasias • Hypersensitivity reactions	• Used for initial parenteral therapy in patients with bacterial pyelonephritis who are allergic to cephalosporins • Used in combination with a cephalosporin in severe UTI • Monitor blood levels and kidney function if therapy extends > 48 hours • Measure trough level before the third dose to minimize toxicity. The efficacy is confirmed by measuring peak levels after the second dose. Consult a specialist if trough levels are high • Target plasma level: Peak > 8mg/l, Trough < 1mg/l
Amikacin	Neonates • 15 mg/kg/dose daily on the first day then 18mg/kg/day Children 10 years and older • 20mg/kg/dose on the first day and then 15mg/kg/dose daily		• If trough level > 5mg/l increase dosage intervals to 36–48 hours and measure after 2 further doses given • Reduce dose in renal impairment • Use with caution in neonates
Folate antagonist			
Trimethoprim/ sulfamethoxazole	• 8–10 mg/kg/day, divided every 12 hours	• Diarrhea, nausea/vomiting, • Hypersensitivity reaction including Steven Johnson and toxic epidermal necrolysis • Photosensitivity • Skin rash • Blood dyscrasias	• Not recommended in infants under 6 weeks • Risk of kernicterus in jaundiced infants. • Increase fluid intake to reduce risk of crystalluria. • Regular blood count should be done during prolonged therapy.
Fluoroquinolones			
Ciprofloxacin	Neonates • Oral 15 mg/kg/dose 12 hourly in the first 4 weeks of life, 8 hourly thereafter • IV infusion10 mg/kg 12 hourly in the first 4 weeks of life, 8 hourly thereafter Children 1 month and older • Oral 5–10 mg/kg/dose 12 hourly • IV 4–7 mg/kg/dose 12 hourly	• Diarrhea, nausea/vomiting • Arthralgia • Risk of tendinitis and tendon rupture, Headache, dizziness, restlessness • Hypersensitivity reaction including Steven Johnson syndrome • QT prolongation	• **NOT** routinely recommended for UTIs • Only considered when benefit outweigh risk in complicated cases due to damage to cartilage of weight-bearing joints • Active against Gram-positive and negative organisms, including ESBL producing *Enterobacteriaceae, P. aeruginosa.*
Urinary tract antiseptics			
Nitrofurantoin	• 1–2 mg/kg divided 6 hourly	• Diarrhea, nausea/vomiting • Headache, dizziness • Respiratory hypersensitivity reactions • Peripheral neuropathy • Hemolysis in patients with G6PD deficiency	• May be used to treat cystitis but not pyelonephritis due to limited tissue penetration • Not effective against *P.aeruginosa* and *Proteus species.* • Contraindicated in infants due to possibility of hemolytic anemia
Other antibacterial agents			
Fosfomycin	• Female children over 5 years 2 g as a single dose	• Minor and infrequent skin rash and gastrointestinal disturbances	• Absorption is reduced by food and should be taken 2 hours before the next meal. • Active against Gram-positive and negative organisms, including ESBL producing *Enterobacteriaceae.* • Off-label use in male patients

(10–14 days) in febrile children, and a shorter course (3–5 days) for immune-competent children without fever.[36]

Various combinations of empiric therapy are effective in treating UTIs in children without genitourinary abnormalities. First line agents usually include 3rd generation cephalosporins (cefpodoxime, cefixime, cefotaxime and ceftriaxone), aminoglycosides (gentamicin and amikacin), and penicillin combinations (amoxicillin-clavulanic acid).[37,38,39] The 3rd generation cephalosporins and aminoglycosides should however not be used in patients with a urinary catheter or anatomical abnormality where infection with *Enterococcus* is suspected.[40] In such patients, amoxicillin or ampicillin should be added to the therapy.[41,42,43,44,45] Hydration status and renal function should be assessed in patients who are treated with aminoglycosides.[46,47,48] Once-daily parenteral administration of gentamicin or ceftriaxone may avoid the need for hospital

admission in select patients (e.g., children older than 3 months who are unable to tolerate oral therapy, well hydrated, absence of urological abnormalities, and whose caretakers will be able to adhere to an outpatient regimen).[49] Oral agents excreted in the urine but not achieving therapeutic serum or parenchymal concentrations (nalidixic acid, nitrofurantoin) should not be used to treat pyelonephritis or urosepsis in febrile infants and young children.[50]

Amoxicillin, ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) are no longer recommended as 1st line agents due to the high resistance rate of *E.coli*. Nevertheless, current South African guidelines still recommend oral amoxicillin-clavulanic acid 30 mg/kg/dose amoxicillin component 8 hourly in the management of uncomplicated paediatric UTIs. Neonates and acutely ill infants should be treated with intravenous amoxicillin-clavulanic acid 25 mg/kg/dose 8 hourly or ceftriaxone 80 mg/kg daily. If no clinical improvement is noted after 24 hours, gentamicin 5 mg/kg should be added. In a child with a penicillin and cephalosporin allergy, treatment with TMP-SMX may be considered.[40,41,42]

Fluoroquinolones are effective against *E. coli*, and resistance in children is rare. Its routine use in patients under 18 years is not advocated due to the potential damage to growing cartilage and bone of weight-bearing joints.[51] The American Academy of Paediatrics (AAP) Committee on Infectious Diseases recommends that the use of ciprofloxacin in children be limited to UTIs caused by *Pseudomonas aeruginosa* or other multidrug-resistant, gram-negative bacteria.[52]

Symptomatic relief of dysuria consists of increasing fluid intake and paracetamol 15 mg/kg/dose. Nonsteroidal anti-inflammatory drugs (NSAIDs) should only be given when necessary. Glucocorticosteroids may decrease renal scarring in paediatric pyelonephritis.[53] If voiding symptoms are severe and persistent, phenazopyridine hydrochloride (Pyridium) could be added for a maximum of 48 hours due to possible risk of hemolytic anemia.[45]

Asymptomatic bacteriuria does not require treatment and use of long-term prophylactic antibiotic therapy is not recommended. Prophylactic antibiotics do not reduce the risk of urinary tract infections in children with mild to moderate vesicoureteral reflux, however severe forms of this structural abnormality may benefit.[53,54] The currently available antibiotics used to treat children with UTIs in South Africa is summarised in Table 1.

Conclusion

The prevalence of UTI in children varies widely by age, gender and circumcision status. Fever may often be the only sign of a UTI in infants and younger children, and should therefore be evaluated to exclude urinary tract infections. Older children may complain of abdominal pain, back pain, frequency, nausea and new onset of urinary incontinence. Accurate and reliable diagnosis requires a thorough physical examination measuring blood pressure, checking growth parameters, abdominal and genital examination and a search for other sources of fever. The treatment choice should be guided by local resistance patterns and empiric protocols in the absence of known causative organisms. Definitive therapy is based on the results from urine culture and sensitivities. Cephalosporins should be used as first line oral therapy in children with uncomplicated UTIs. Intravenous cephalosporins and aminoglycosides are first line parenteral empiric therapy. A nephrologist should be consulted when there is poor response to therapy, persistent positive culture and/or fever, obstruction, renal failure, vesicoureteral reflux, renal scarring, anatomic abnormalities, renal calculi or if invasive imaging procedures are considered.

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