

Managing urinary tract infections

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Received: 1 October 2010 / Revised: 25 January 2011 / Accepted: 28 January 2011 / Published online: 16 March 2011
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Abstract Urinary tract infections (UTI) are common in childhood. Presence of pyuria and bacteriuria in an appropriately collected urine sample are diagnostic of UTI. The risk of UTI is increased with an underlying urological abnormality such as vesicoureteral reflux, constipation, and voiding dysfunction. Patients with acute pyelonephritis are at risk of renal scarring and subsequent complications such as hypertension, proteinuria with and without FSGS, pregnancy-related complications and even end-stage renal failure. The relevance and the sequence of the renal imaging following initial UTI, and the role of antimicrobial prophylaxis and surgical intervention are currently undergoing an intense debate. Prompt treatment of UTI and appropriate follow-up of those at increased risk of recurrence and/or renal scarring are important.

Keywords Urinary tract infection · Vesicoureteric reflux · Management

Introduction

Urinary tract infection (UTI) is a common illness in children, with overall prevalence ranging from 2% to 8% throughout childhood [1–3]. It can be associated with long-

term sequela of renal scarring, which may cause hypertension, proteinuria, pregnancy-related complications, or even progressive renal failure. The risk of recurrent UTI in children has been estimated to be 12–30% in the first 6–12 months after the initial UTI [4, 5]. Predisposing factors for recurrence include vesicoureteral reflux and dysfunctional elimination [6–8]. *Escherichia coli* remains the most common organism causing UTI in children (60–92%). Other common organisms include *Klebsiella*, *Proteus*, *Enterococcus*, and *Enterobacter* spp. [9–11]. Less common organisms such as *Pseudomonas*, Group B *Streptococcus*, and *Staphylococcus aureus* are seen with increased frequency in patients with anatomical defects, kidney stones, following genitourinary surgery or bladder catheterization, and following repeated courses with antibiotic treatments [3, 8]. The pathogenetic mechanism of UTI is thought to be an ascending infection from periurethral organisms in children older than the neonatal period. Factors contributing to infection include bacterial virulence factors as well as host defense mechanisms. Clinical differentiation of the site of UTI is important. Pyelonephritis, or upper UTI, refers to infection of the renal parenchyma, which manifests as flank pain, fever, and systemic manifestations such as nausea, vomiting, or diarrhea. These patients are at risk of renal scarring. Cystitis, or lower UTI, is infection of the urinary bladder, which usually presents with symptoms of bladder irritation, dysuria, urinary frequency or hesitancy, and low-grade abdominal pain in the absence of systemic manifestations such as fever. Clinical manifestations of UTI are also age dependent. Apart from fever, older children can express and localize flank pain associated with pyelonephritis compared with infants with pyelonephritis, who may present with a combination of symptoms that include fever, irritability, excessive crying, diarrhea, and poor feeding. In young infants

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and children, fever is of special importance as a clinical marker of renal parenchymal involvement (pyelonephritis). As acknowledged by the American Academy of Pediatrics (AAP) in its practice parameters, the presence of high fever ($\geq 39^{\circ}\text{C}$) with clinical diagnosis of UTI is an important indicator of pyelonephritis compared with no fever ($\leq 38^{\circ}\text{C}$) in those with cystitis [12, 13]. Indirect tests of inflammation [elevated peripheral white blood cell (WBC) count, elevated C-reactive protein (CRP)] can provide helpful guidance. The use of dimercaptosuccinate (DMSA) scan to differentiate the site of infection is discussed separately.

Diagnosing UTI requires appropriate collection of uncontaminated urine sample for analysis and culture. The technique of obtaining the urine can affect sample quality. It is recommended to collect urine by clean catch in children who are toilet trained. In infants and younger children, urine should be obtained by urinary catheterization or suprapubic aspiration. Collection of urine with adhesive bags to the perineal area has no role in diagnosing UTI due to the high risk of contamination. For a prompt diagnosis, urine is examined by dipstick and microscopy. Urine dipstick is an inexpensive and a readily available technique. The presence of either leukocyte esterase (LE) and/or nitrite is interpreted as a positive dipstick test [14], whereas blood and protein are poor indicators of UTI. Urine microscopy is performed to look for the presence of WBC or bacteria, and its sensitivity and specificity are better with uncentrifuged urine and Gram staining of the sample. Urine Gram stain for bacteria has a better sensitivity (91%) and specificity (96%) than all other rapid tests used alone or in combination [14] and when positive can guide therapy in children suspected of having UTI. When uncentrifuged urine is examined microscopically, pyuria is defined by ≥ 10 WBC/mm³ and bacteriuria by the presence of any bacteria per 10 oil immersion field of Gram-stained smear. Table 1 summarizes data from a recent meta-analysis by Williams et al. [14] evaluating rapid urine tests and comparing the accuracy of dipstick with microscopy. They concluded that Gram stain is the single best rapid test but still cannot replace urine culture. The study also concluded that either LE or nitrite positivity can be interpreted as positive dipstick testing.

Urine culture remains the reference standard for diagnosing UTI. However, because it requires a minimum of 18 hours before a result is known, the rapid tests are often used

to guide the initial management. Accepted colony count criteria for a probable UTI diagnosis are summarized in Table 2 [15, 16]. Increasing the acceptable colony count for UTI diagnosis has been suggested to decrease the false positive rate [17].

Asymptomatic bacteriuria

Asymptomatic bacteriuria (ABU) is defined as the growth of a significant number of a single organism [often $> 100,000$ colony-forming units (CFU/ml)] from a urine sample of an asymptomatic child with no pyuria. It is often an incidental finding and can be demonstrated on repeat urine cultures. The bacterium isolated is most often an *E. coli* strain of low virulence that colonizes the urinary tract and does not have significant ability to damage the kidneys [18]. Antibiotics should not be given to eradicate ABU [19–22]. ABU is also observed in children with neurogenic bladder, particularly if the patient is on clean intermittent catheterization, but studies have not shown increased risk of renal scarring or the need for prophylactic antibiotics in this group [19]. Patients with neurogenic bladder very often also have increased number of WBC in their urine, which makes UTI diagnosis difficult.

Renal imaging in UTI

The rationale for renal imaging is to identify risk factors and abnormalities of the genitourinary tract that can be modified to decrease the likelihood of recurrent UTI and renal scarring.

Renal ultrasound

Renal ultrasound is useful for detecting renal abscess, hydronephrosis, congenital abnormalities, and sometimes stones. It has a lower sensitivity for diagnosing pyelonephritis than DMSA; abnormalities compatible with pyelonephritis were reported in 20–69% of patients by ultrasound compared with 40–92% by DMSA [23]. Ultrasound has limited usefulness for assessing the presence of renal scarring; a study by Ahmed et al. [24] showed that renal

Table 1 Sensitivity and specificity of rapid urine tests. Adapted with modification from [14], with permission

	WBC	Gram stain	LE	Nitrite	Either LE or nitrite	Both LE and nitrite
Sensitivity	74%	91%	79%	49%	88%	45%
Specificity	86%	96%	87%	98%	79%	98%

WBC white blood cells, LE leukocyte esterase

Table 2 Diagnosing urinary tract infection (UTI) by urine culture

Collection method	Colony count (CFU/ml)	Probability of infection (%)
Suprapubic aspiration	Any growth	>99%
Catheterization	$>10^5$	95%
	10^4 - 10^5	Infection likely
Clean-catch, midstream urine	$>10^4$ (boy)	Infection likely
	$\geq 10^5$ (girl) (3 specimens)	95%
	$\geq 10^5$ (girl) (2 specimens)	90%
	$\geq 10^5$ (girl) (1 specimen)	80%

CFU colony-forming units

Adapted with modification from [16], with permission

ultrasound is not as sensitive in comparison with DMSA scan when used to detect renal scarring in children being worked up for hypertension.

Voiding cystourethrogram

Voiding cystourethrogram (VCUG) is the main diagnostic modality for identifying vesicoureteral reflux (VUR). It can be performed immediately after antibiotic treatment is completed and the patient is asymptomatic. It requires urinary catheterization. VUR grading has been suggested by the International Reflux Study (IRS) into 5 grades [25]. This grading system has been used in an effort to predict the outcome of children with different grades of reflux, standardize management, and compare outcomes of different management approaches. Radionuclear cystography (RNC) has been primarily used to reduce radiation exposure for children during follow-up for VUR or after surgical correction to verify resolution. However, tailored low-dose fluoroscopic VCUG can result in gonadal radiation exposure comparable with that reported with the radionuclide technique. RNC grades VUR into mild, moderate, and severe. Therefore, because of its inability to grade VUR or reveal anatomic defects, it is not used as an initial test to diagnose VUR.

DMSA (dimercaptosuccinic acid) renal scan

DMSA is the gold standard for diagnosing acute pyelonephritis and renal scars. When used at the time of acute illness, it can help confirm acute pyelonephritis, if in doubt. However, it does not distinguish lesions that will spontaneously resolve from those which will cause renal scarring. Also, the differentiation of changes secondary to acute pyelonephritis from those due to preexisting renal scars can be difficult. For these reasons, a delay of 4–6 months is needed following acute pyelonephritis to allow acute reversible lesions to resolve in order to diagnose renal scarring [26].

Rationale for imaging

The best approach for imaging studies in children with UTI is debatable because of the doubtful evidence and concerns

over the actual value of these studies in altering the management and final outcome. The AAP, in its practice parameters published in 1999, recommends renal ultrasound and VCUG or RNC be performed in any infant or child (2 months to 2 years of age) after a first UTI [12]. In 2007, in an effort to reduce the imaging burden of UTI work-up, the National Institute for Health and Clinical Excellence (NICE) of Great Britain published its recommendations on a more selective approach for renal imaging after UTI [27]. These recommendations are primarily based on patient age, response to antibacterial treatment, and typical versus atypical UTI. Further details on the guidelines are shown in Table 3. However, an argument has been made that this very selective approach can lead to delayed diagnosis of VUR and congenital abnormalities in these children [28, 29]. A retrospective analysis by Tse et al. revealed that selective imaging by NICE guidelines would have left a significant number of undiagnosed VUR and renal scars in infants <6 months of age [30]. More studies are needed to validate the NICE guidelines.

Another suggested approach to imaging in VUR is to replace the VCUG with a DMSA scan from the top-down approach; VCUG can then be performed if ultrasound and DMSA are abnormal [31, 32]. However, it has been shown recently that DMSA scan has limited ability in diagnosing VUR and replacing VCUG for evaluating children with their first UTI. Furthermore, the issue of differences in methodology used by different medical centers and the interobserver variability in scan interpretation need to be kept in mind [33]. A more definitive answer to the question of imaging is still lacking, and more evidence is needed to validate any of the current suggested approaches. The treating clinician should be aware of the available renal imaging options and their appropriate use in a particular child, which depends on patient age, VUR severity, presence or absence of renal scarring, and UTI frequency.

UTI treatment

UTI treatment depends on infection location (cystitis vs. pyelonephritis), patient's age, severity of presentation, and

Table 3 National Institute for Health and Clinical Excellence (NICE) imaging guidelines

	Responds well to treatment within 48 h	Atypical UTI ^a	Recurrent UTI ^b
Age < 6 months	Ultrasound ^c	Ultrasound, DMSA and VCUG	Ultrasound, DMSA and VCUG
Age 6 months–3 years	None	Ultrasound and DMSA ^d	Ultrasound and DMSA ^d
Age > 3 years	None	Ultrasound	Ultrasound and DMSA

UTI urinary tract infection, DMSA dimercaptosuccinate, VCUG voiding cystourethrogram

^a Non-*Escherichia coli* UTI: seriously ill, poor urine flow, abdominal or bladder mass, raised creatinine, septicemia, failure to respond to treatment with suitable antibiotics within 48 h

^b Two or more episodes of UTI with acute pyelonephritis/upper urinary tract infection, or one episode of UTI with acute pyelonephritis/upper urinary tract infection plus one or more episode of UTI with cystitis/lower urinary tract infection, or

three or more episodes of UTI with cystitis/lower urinary tract infection

^c If ultrasound is abnormal, consider a VCUG

^d Consider VCUG if dilatation on ultrasound, poor urine flow, non-*E. coli* infection, family history of VUR

the antimicrobial resistance pattern in the community. Empiric therapy for UTI should be initiated after appropriate urine specimen for culture has been obtained. Children <24 months of age suspected to have UTI should be treated as having pyelonephritis, whereas a more symptom-based approach can be followed in older children.

Treatment promptness

It is believed that prompt antibiotic treatment of UTI diminishes the risk of renal scarring [12, 34]. However, two recent studies, by Hewitt et al. [35] and Doganis et al. [36], demonstrated that early treatment (< 1 day of fever) of acute pyelonephritis in infants and young children had no significant effect on the incidence of subsequent renal scarring when compared with children treated after 24 h. However, Doganis et al. showed that early and appropriate treatment, especially during the first 24 h after symptom onset, may diminish the likelihood of renal involvement during the acute phase of the infection [36]. The study included a smaller number of patients treated after 4 days compared with patients treated in <1 day. Also, it should still be kept in mind that even though these studies showed no evidence of renal damage following delayed treatment, it is not advisable to delay treatment of a sick patient when UTI is diagnosed. Patients with pyelonephritis can have

complications other than scarring when treatment is delayed, such as sepsis and abscess formation.

Oral versus parenteral therapy

The AAP practice parameter guidelines published in 1999 recommend that well-appearing children between 2 months and 2 years of age with UTI can be treated with orally or parenterally administered antibiotics [12]. A 2007 Cochrane Review of 23 randomized and quasirandomized controlled studies showed no significant difference in persistent kidney damage at 6–12 months or in fever duration between orally administered antibiotic therapy for 10–14 days and intravenously administered (IV) antibiotic therapy for 3 days followed by oral therapy for 10 days. Also, no significant difference in persistent kidney damage was found between initial IV therapy (3–4 days) followed by oral therapy and IV therapy for the entire treatment duration (7–14 days) [37]. Few other studies had similar conclusions when oral antibiotics were compared with parenteral therapy. A multicenter randomized controlled trial by Montini et al. showed that oral therapy was as effective as IV therapy followed by oral therapy for managing the first UTI episode [38]. However, most of these studies excluded high-risk children, such as those with significant renal scarring or genitourinary abnormali-

Table 4 Oral antibiotics for treating cystitis

Antibiotic	Dose
Trimethoprim (TMP)-sulfamethoxazole	8 mg (TMP)/kg/day divided every 12 h
Nitrofurantoin	5–7 mg/kg/day divided every 6 h
Amoxicillin	25–45 mg/kg/day divided every 12 h
Amoxicillin-clavulanate	25–45 mg (amoxicillin)/kg/day divided every 8–12 h
Cephalexin	25–50 mg/kg/day divided every 6 h
Cefixime	8 mg/kg/day divided every 12 h

ties. These high-risk children need to be identified and might benefit from initial parenteral therapy. In general, orally administered antibiotics can be used effectively on an outpatient basis to treat acute pyelonephritis in children >2–3 months who are clinically stable [37, 39]. Suitable antibiotic choices are listed in Table 5. For lower UTI (cystitis), orally administered antibiotics for a short period (2–4 days) are generally effective.

Indications for hospitalization of any child with UTI include clinical urosepsis, laboratory evidence of bacteremia, immunocompromised patient, intolerance to oral intake, lack of adequate outpatient follow-up, or failure to respond to outpatient therapy. Managing febrile infants <2–3 month has not been well studied because these patients are often excluded from randomized controlled trials. They have a 10% concomitant risk of bacteremia [36], which prompts hospitalization and IV treatment with antibiotics until the systemic signs have resolved [3, 40, 41]. Complete septic work-up should be done in patients <1 month because UTI is most often secondary to hematogenous seeding rather than ascending infection.

Antibiotic selection

The choice of empirical antibiotics is guided by local resistance patterns, but coverage for *E. coli* as the most common infective organism should be considered. The North American Urinary Tract Infection Collaborative Trial report published in 2006 showed considerable *E. coli* resistance to β -lactam antibiotics (37.7%) and trimethoprim–sulfamethoxazole (21.3%) [42], which makes these agents inadequate first-line choices for treating serious UTI [43, 44]. Prelog et al., in a retrospective study of children with febrile UTI, showed that β -lactam antibiotics and trimethoprim-resistant *E. coli* were more commonly seen in children with (35.8%) than in those without (25.8%) VUR [44]. However, *E. coli* remains largely sensitive to third-generation cephalosporins (ceftriaxone, cefixime), aminoglycosides, and nitrofurantoin [43, 45]. Final antibiotic choice should be based on pathogen identification and sensitivity from urine culture. In infants <1 month, the most likely pathogens are *E. coli* and *E. faecalis*, which require empiric therapy with a β -lactam antibiotic and an aminoglycoside.

Orally administered antibiotics Second- and third-generation cephalosporins are appropriate first-line treatment options for pyelonephritis. Alternatively, amoxicillin–clavulanate, trimethoprim–sulfamethoxazole (TMP-SMX), and first-generation cephalosporins can be used with caution due to increasing resistance of *E. coli*. Fluoroquinolones (ciprofloxacin) are effective for *E. coli* but should not be used as first-line agents due to their questionable safety in children. Ciprofloxacin should be reserved for UTI caused by *P. aeruginosa* or other multi-drug-resistant organisms.

Parenteral therapy Third- or fourth-generation cephalosporins and aminoglycosides are appropriate for empiric treatment. When enterococcal UTI is suspected (urinary catheter, instrumentation of the urinary bladder, or genitourinary abnormalities), ampicillin should be included in treatment options. Gentamicin can be used parenterally as an adjunctive treatment in resistant organisms. However, its nephrotoxic properties limit its use. When gentamicin used, therapeutic levels and kidney function should be monitored (Table 6). After urine culture results are available, antibiotic treatment could be adjusted according to the sensitivity of the identified pathogen.

Treatment duration and response

The optimal treatment duration for pyelonephritis is 7–14 days, depending on administration route. In cases of severe pyelonephritis (acute lobar nephronia), prolonged parenteral therapy may help prevent progression to abscess [1]. For treating acute bacterial cystitis, several studies have shown that short treatment courses of 2–4 days are as effective as 7–14 days in eradicating lower UTI in children [46]. Treatment response in most patients is often noted within 24–48 h of antibiotic initiation. Children with worsening clinical condition (other than fever) might need imaging to rule out abscess formation, urinary stones, or obstruction. Revising the antibiotic selection might be needed. Repeat urine cultures after treatment are not needed in children who show clinical response to treatment [47, 48]. Children on prophylactic antibiotics for VUR might present a challenge to treatment as they are more likely to

Table 5 Orally administered antibiotics for treating pyelonephritis

Antibiotic	Dose
Cefixime	8 mg/kg/day divided every 12 h
Cefdinir	14 mg/kg/day divided every 12 h
Amoxicillin-clavulanate	25–45 mg (amoxicillin)/kg/day divided every 8–12 h
Ciprofloxacin	20–30 mg/kg/day divided every 12 h

Table 6 Parenteral antibiotics for treating pyelonephritis

Antibiotic	Dose
Ampicillin	100 mg/kg/day divided every 6 h
Cefotaxime	100-200 mg/kg/day divided every 8 h
Ceftriaxone	50-100 mg/kg/day divided every 12 h
Cefepime	100 mg/kg/day divided every 12 h
Gentamicin	7.5 mg/kg/day divided every 8 h

have UTI with a resistant organism [11, 49]. This is especially the case when prophylactic cephalosporins are used. Resistance has also been found to third-generation antibiotics in these children, but sensitivity to gentamicin remained high. This should be considered when choosing an antibiotic for these children, especially those who are acutely ill or not responding to initial empiric therapy. Children with anatomical defects, following genitourinary surgery, or repeated UTI and antibiotic courses, are more likely to have other causative organisms, such as *Pseudomonas*, Group B *Streptococcus*, *S. aureus*, or *S. epidermidis*, which should also be taken into consideration when these patients do not respond adequately to initial empiric therapy.

Antimicrobial prophylaxis

The role of VUR in causing UTI and the use of antimicrobial prophylaxis to prevent UTI with and without VUR is controversial. Regardless, the use of antimicrobial prophylaxis has been a standard practice for many decades. In 2006, a Cochrane Review by Williams et al. [50] identified eight randomized studies (618 children) that compared antibiotics with placebo or no treatment to prevent recurrent UTI. This analysis showed that antibiotics decreased the risk of positive urine culture compared with placebo. However, the authors concluded that more evidence in the form of properly randomized double-blinded trials is needed to support the routine use of antibiotic prophylaxis in preventing recurrent

UTI. Recently, there have been six randomized trials on antimicrobial prophylaxis for UTI [51–56], Table 7. Three of those included children with and without VUR [51, 54, 55]. Overall, these studies included patients from 0 to 18 years of age, with grades I–V VUR, if present. Garin et al. [51] and Montini et al. [54] reported no benefit with prophylaxis in children with and without VUR (grades I–III). The third study, by Craig et al. [55], which was placebo-controlled, showed a reduction in the absolute risk of UTI (6 percentage points) that did not vary with any stratifying variable (age, sex, reflux status, history of more than one UTI, or susceptibility of the causative organism for TMP-SMX). The other three randomized trials of antimicrobial prophylaxis for UTI included only patients with VUR grades I–IV, and patients' ages ranged from 0 to 3 years [52, 53, 56]. Roussey et al. [52] found no benefit to antibiotic prophylaxis in low-grade VUR except in boys with grade III reflux. Pennesi et al. [53] found no difference in UTI recurrence between prophylaxis and no prophylaxis in all patients <30 months. The Swedish Reflux Trial [56] studied 203 children (1–2 years of age) with grades III–IV reflux openly randomized into three groups: low-dose antibiotic prophylaxis, endoscopic therapy, and surveillance. The study demonstrated that UTI recurrence rate in girls >1 year with dilating VUR was higher than in boys and that this rate can be decreased with antibiotic prophylaxis and endoscopic treatment. There was no difference between the prophylaxis and endoscopic treatment groups. Fifty-seven percent of patients in the surveillance group suffered a UTI recurrence during follow-up. The study also showed that girls had a significantly higher rate of new renal damage on DMSA than boys at 2 years. Renal damage was most common in the surveillance group and showed a strong association with recurrent febrile UTI [57]. The results of these studies should be interpreted with caution because of some design-related limitations.

In 2007, NICE published its recommendations that health-care professionals in the United Kingdom do not use antibiotic prophylaxis routinely in infants and children following first-time UTI, and only selectively in recurrent UTI [27]. The

Table 7 Randomized trials on antimicrobial prophylaxis for urinary tract infections (UTI)

Author and year	Patient age	Total number of patients in study	VUR status	Number of patients with VUR	VUR grade	Follow-up (months)
Garin et al. [51]	1 month-18 years	218	±VUR	113	I-III	12
Roussey-Kesler et al. [52]	1 month-3 years	225	+VUR	225	I-III	18
Pennesi et al. [53]	0-30 months	100	+ VUR	100	II-IV	24- 48
Montini et al. [54]	2 months-7 years	338	±VUR	128	I-III	12
Craig et al. [55]	0-18 years	576	±VUR	243	I-V	12
Swedish Reflux Trial [56]	1-2 years	203	+VUR	203	III-IV	24

VUR vesicoureteral reflux

Table 8 Initial management of a child <1 year old with vesicoureteral reflux (VUR) according to American Urological Association (AUA) guidelines

	Continuous antibiotic prophylaxis			
		Standard	Recommended	Option
VUR diagnosed after febrile UTI	All grades	–	✓	–
VUR diagnosed through screening	Grades I & II	–	–	✓
	Grades III- V	–	✓	–

American Urological Association (AUA) published its guidelines on primary VUR management in September of 2010 based on the current evidence related to VUR management in children [6]. These guidelines are summarized in Tables 8, 9, and 10. The initial management of a child with VUR (Tables 8 and 9) is stratified by age, with a more conservative approach in children <1 year because of their increased morbidity with pyelonephritis and higher incidence of renal scarring. The statements made by AUA are graded with respect to the degree of flexibility in application. Standard is the most rigid statement policy; Recommendation has significantly less rigidity, being a statement with sufficient evidence to advocate for a particular clinical approach; Option offers the most flexibility when there is evidence of relatively equal strength to support more than one approach.

In view of all these studies and recommendations, VUR management is a subject of constant debate. The need for higher-quality evidence to guide management is increasing. The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) funded by the US National Institutes of Health (NIH) is underway. It is a double-blind, randomized, placebo-controlled trial that started enrolling in 2007, which will evaluate the role of antimicrobial prophylaxis in children with grades I–IV VUR diagnosed after febrile UTI. Until more evidence-based practices evolve, the treating physician should be cautious when treating children with risk factors for recurrent UTI, including VUR. The clinician must decide whether the benefit of antibiotic use outweighs the risk and when surgical intervention might be a preferred option.

Table 9 Initial management of a child >1 year old with vesicoureteral reflux (VUR) according to American Urological Association (AUA) guidelines

	Continuous antibiotic prophylaxis		
	Standard	Recommended	Option
No recurrent febrile UTI, BBD or renal cortical anomalies	–	–	✓
Recurrent febrile UTI, BBD, or renal cortical anomalies	–	✓	–

BBD bladder and bowel dysfunction

Prophylactic antimicrobial choice

Antibiotics commonly used include TMP-SMX, trimethoprim, nitrofurantoin, and first-generation cephalosporins. Amoxicillin can be used in children <2 months, because TMP-SMX is contraindicated in this age group (Table 11).

Prophylaxis limitations

Antimicrobial resistance is a major concern with antibiotic prophylaxis. Cheng et al. [49], in a retrospective analysis, found that infection was less common in children on antibiotic prophylaxis compared with their initial episodes of UTI. Cephalosporins as prophylactic antibiotics compared with TMP-SMX are more likely to be associated with breakthrough UTI caused by extended-spectrum β-lactamase-producing organisms [49]. This could present as a problem of increasing difficulty of prescribing appropriate antibiotics when children present with recurrent UTI. Other problems with prophylaxis include compliance and parental concern over long-term antibiotic administration.

Surgical treatment of VUR

Surgical treatment is usually reserved for patients with high-grade VUR, recurrent UTI despite antibiotic prophylaxis, and noncompliance with prophylactic antibiotics. Open surgery has largely been replaced by endoscopic and laparoscopic techniques. Endoscopic treatment involving subureteral or intraureteral injection of a bulking agent with dextranomer/ hyaluronic acid (Deflux®) is suggested as first-line treatment. Success rates are 98.1% for open and 83% for endoscopic surgery after injection [6]. The most recent AUA guidelines gave the option of surgical intervention, including open and endoscopic surgery, at the time of the initial diagnosis. The decision is affected by the patient’s age, kidney status, reflux grade, and parental wishes [6]. The Swedish Reflux Trial report on VUR outcome demonstrated that endoscopic treatment resulted in a significantly higher resolution or downgrading of dilating VUR compared with prophylaxis and surveillance [58]. It also raised concern over the common reappearance of dilating VUR after 2 years from endoscopic treatment.

Table 10 Breakthrough urinary tract infection (BT-UTI) management according to American Urological Association (AUA) guidelines

Clinical scenario	Recommendation (R)/ Option (O)
Symptomatic BT-UTI	R: Change of therapy guided by scenario
Patient on CAP with febrile BT-UTI	R: Consider open or endoscopic surgical intervention
Patient on CAP with single febrile BT-UTI without evidence of existing or new renal cortical abnormalities	O: change to alternative antibiotics is an option before surgical intervention
Patient not on CAP with febrile BT-UTI	R: Initiation of CAP
Patient not on CAP with nonfebrile UTI	O: Initiation of CAP
All patients with BT-UTI	O: Surgical intervention

CAP continuous antibiotic prophylaxis

Conclusion

UTI is a common infection in children, with a potential risk for complications such as renal scarring. Appropriate UTI diagnosis and management is important. Management is aimed at treating the acute episode as well as preventing recurrences. Renal ultrasound after a first UTI is helpful in diagnosing some underlying congenital abnormalities that increase recurrence risk and that may need surgical intervention. VCUG and the DMSA renal scan remain the gold standards for diagnosing VUR and renal scarring, respectively. Decisions regarding antimicrobial prophylaxis or surgical intervention in children with VUR are primarily based on patient age, VUR severity, presence of renal scarring, UTI frequency, and voiding dysfunction.

Multiple-choice questions

(Answers appear following the reference list)

- Which one of the following statements regarding UTI diagnosis is true?
 - Clean-catch urine sample can be used in all children
 - Urethral catheterization or suprapubic aspiration should be performed in infants and newborn

- Urethral catheterization has a lower likelihood of contamination compared with suprapubic aspiration
 - Periurethral adhesive bag can be used in boys but not girls because of contamination risk
 - Any bacterial growth from a catheterized urine sample is considered significant
- Of the following, which one is the most specific test for UTI by dipstick?
 - LE alone
 - Nitrite alone
 - Protein and blood
 - LE and nitrite
 - Protein and LE
 - Which one of the following characterizes asymptomatic bacteriuria?
 - Pyuria is present
 - Most commonly caused by *Pseudomonas Aeruginosa*
 - Antibiotic treatment is indicated
 - Can be a normal finding in children with neurogenic bladder
 - Increased risk of scarring if antibiotic prophylaxis is not used
 - Which of the following tests is the current gold standard for diagnosing renal scarring?
 - Ultrasound examination
 - Intravenous pyelography
 - DMSA renal scan
 - CT scan
 - Radionuclear cystography (RNC)

Table 11 Prophylactic antimicrobial agents

Antibiotic	Dose
Trimethoprim (TMP)–sulfamethoxazole	2 mg TMP/kg/day daily
Nitrofurantoin	1–2 mg/kg/dose daily
Cephalexin	10 mg/kg/dose daily
Amoxicillin	10 mg/kg/dose daily

References

- Uhari M, Nuutinen M (1988) Epidemiology of symptomatic infections of the urinary tract in children. *BMJ* 297:450–452
- Dunand BA (2009) Urinary Tract Infections. In: Avner ED HW, Niaudet P, Yoshikawa N. (ed) *Pediatric Nephrology*. Springer
- Bell LE, Mattoo TK (2009) Update on childhood urinary tract infection and vesicoureteral reflux. *Semin Nephrol* 29:349–359
- Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R (2007) Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA* 298:179–186
- Dai B, Liu Y, Jia J, Mei C (2010) Long-term antibiotics for the prevention of recurrent urinary tract infection in children: a systematic review and meta-analysis. *Arch Dis Child* 95:499–508
- Peters CA, Skoog SJ, Arant BS Jr, Copp HL, Elder JS, Hudson RG, Khoury AE, Lorenzo AJ, Pohl HG, Shapiro E, Snodgrass WT, Diaz M (2010) Summary of the AUA guideline on management of primary vesicoureteral reflux in children. *J Urol* 184:1134–1144
- Shaikh N, Ewing AL, Bhatnagar S, Hoberman A (2010) Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics* 126:1084–1091
- Bensman A, Dunand O, Ulinski T (2009) Urinary Tract Infections. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N (Eds) *Pediatric Nephrology*. Springer, Berlin, pp 1299–1309
- Akram M, Shahid M, Khan AU (2007) Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in J N M C Hospital Aligarh, India. *Ann Clin Microbiol Antimicrob* 6:4
- Chakrapurakal R, Ahmed M, Sobithadevi DN, Chinnappan S, Reynolds T (2010) Urinary tract pathogens and resistance pattern. *J Clin Pathol* 63:652–654
- Lutter SA, Currie ML, Mitz LB, Greenbaum LA (2005) Antibiotic resistance patterns in children hospitalized for urinary tract infections. *Arch Pediatr Adolesc Med* 159:924–928
- American Academy of Pediatrics (1999) Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on quality improvement. Subcommittee on urinary tract infection. *Pediatrics* 103:843–852
- Winberg J, Andersen HJ, Bergstrom T, Jacobsson B, Larson H, Lincoln K (1974) Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatr Scand Suppl*:1–20
- Williams GJ, Macaskill P, Chan SF, Turner RM, Hodson E, Craig JC (2010) Absolute and relative accuracy of rapid urine tests for urinary tract infection in children: a meta-analysis. *Lancet Infect Dis* 10:240–250
- Keren R, Carpenter MA, Hoberman A, Shaikh N, Matoo TK, Chesney RW, Matthews R, Gerson AC, Greenfield SP, Fivush B, McLurie GA, Rushton HG, Canning D, Nelson CP, Greenbaum L, Bukowski T, Primack W, Sutherland R, Hosking J, Stewart D, Elder J, Moxey-Mims M, Nyberg L (2008) Rationale and design issues of the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study. *Pediatrics* 122(Suppl 5):S240–S250
- Hellerstein S (1982) Recurrent urinary tract infections in children. *Pediatr Infect Dis* 1:271–281
- Coulthard MG, Kalra M, Lambert HJ, Nelson A, Smith T, Perry JD (2010) Redefining urinary tract infections by bacterial colony counts. *Pediatrics* 125:335–341
- Linshaw M (1996) Asymptomatic bacteriuria and vesicoureteral reflux in children. *Kidney Int* 50:312–329
- Ottolini MC, Shaer CM, Rushton HG, Majd M, Gonzales EC, Patel KM (1995) Relationship of asymptomatic bacteriuria and renal scarring in children with neuropathic bladders who are practicing clean intermittent catheterization. *J Pediatr* 127:368–372
- Bensman A (2002) Should children with asymptomatic bacteriuria (ABU) undergo imaging studies of the urinary tract? *Pediatr Nephrol* 17:76–77
- Hansson S, Martinell J, Stokland E, Jodal U (1997) The natural history of bacteriuria in childhood. *Infect Dis Clin North Am* 11:499–512
- Wettergren B, Hellstrom M, Stokland E, Jodal U (1990) Six year follow up of infants with bacteriuria on screening. *BMJ* 301:845–848
- Lavocat MP, Granjon D, Allard D, Gay C, Freycon MT, Dubois F (1997) Imaging of pyelonephritis. *Pediatr Radiol* 27:159–165
- Ahmed M, Eggleston D, Kapur G, Jain A, Valentini RP, Mattoo TK (2008) Dimercaptosuccinic acid (DMSA) renal scan in the evaluation of hypertension in children. *Pediatr Nephrol* 23:435–438
- Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mobius TE (1985) International system of radiographic grading of vesicoureteric reflux. International reflux study in children. *Pediatr Radiol* 15:105–109
- Ditchfield MR, Summerville D, Grimwood K, Cook DJ, Powell HR, Sloane R, Nolan TM, de Campo JF (2002) Time course of transient cortical scintigraphic defects associated with acute pyelonephritis. *Pediatr Radiol* 32:849–852
- Baumer JH, Jones RW (2007) Urinary tract infection in children, National Institute for Health and Clinical Excellence. *Arch Dis Child Educ Pract Ed* 92:189–192
- Coulthard MG (2008) Is reflux nephropathy preventable, and will the NICE childhood UTI guidelines help? *Arch Dis Child* 93:196–199
- Coulthard MG (2007) NICE on childhood UTI: Nasty processes produce nasty guidelines. *BMJ* 335:463; author reply 463–464
- Tse NK, Yuen SL, Chiu MC, Lai WM, Tong PC (2009) Imaging studies for first urinary tract infection in infants less than 6 months old: can they be more selective? *Pediatr Nephrol* 24:1699–1703
- Herz D, Merguerian P, McQuiston L, Danielson C, Gheen M, Brenfleck L (2010) 5-year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: proof that the top-down approach works. *J Urol* 184:1703–1709
- Lee MD, Lin CC, Huang FY, Tsai TC, Huang CT, Tsai JD (2009) Screening young children with a first febrile urinary tract infection for high-grade vesicoureteral reflux with renal ultrasound scanning and technetium-99 m-labeled dimercaptosuccinic acid scanning. *J Pediatr* 154:797–802
- Ziessman HA, Majd M (2009) Importance of methodology on (99 m)technetium dimercapto-succinic acid scintigraphic image quality: imaging pilot study for RIVUR (Randomized Intervention for Children With Vesicoureteral Reflux) multicenter investigation. *J Urol* 182:272–279
- Hiraoka M, Hashimoto G, Tsuchida S, Tsukahara H, Ohshima Y, Mayumi M (2003) Early treatment of urinary infection prevents renal damage on cortical scintigraphy. *Pediatr Nephrol* 18:115–118
- Hewitt IK, Zucchetto P, Rigon L, Maschio F, Molinari PP, Tomasi L, Toffolo A, Pavanello L, Crivellaro C, Bellato S, Montini G (2008) Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian renal infection study trials. *Pediatrics* 122:486–490
- Doganis D, Sifas K, Mavrikou M, Issaris G, Martirosova A, Perperidis G, Konstantopoulos A, Sinaniotis K (2007) Does early treatment of urinary tract infection prevent renal damage? *Pediatrics* 120:e922–e928
- Hodson EM, Willis NS, Craig JC (2007) Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev*: CD003772
- Montini G, Toffolo A, Zucchetto P, Dall'Amico R, Gobber D, Calderan A, Maschio F, Pavanello L, Molinari PP, Scorrano D, Zanchetta S, Cassar W, Brisotto P, Corsini A, Sartori S, Da Dalt L, Murer L, Zacchello G (2007) Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. *BMJ* 335:386

39. Hoberman A, Wald ER (1997) Urinary tract infections in young febrile children. *Pediatr Infect Dis J* 16:11–17
40. Pantell RH, Newman TB, Bernzweig J, Bergman DA, Takayama JI, Segal M, Finch SA, Wasserman RC (2004) Management and outcomes of care of fever in early infancy. *JAMA* 291:1203–1212
41. Williams G, Craig C. (2008) Diagnosis and Management of Urinary Tract Infections. In: Geary D, Schaefer F (ed) *Comprehensive Pediatric Nephrology*. Mosby, pp 539–548
42. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Weshnoweski B, Johnson J, Noreddin A, Low DE, Karlowsky JA, Hoban DJ (2006) Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents* 27:468–475
43. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnik LP, Johnson J, Noreddin A, Harding GK, Nicolle LE, Hoban DJ (2005) Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents* 26:380–388
44. Prelog M, Schiefecker D, Fille M, Wurzner R, Brunner A, Zimmerhackl LB (2008) Febrile urinary tract infection in children: ampicillin and trimethoprim insufficient as empirical monotherapy. *Pediatr Nephrol* 23:597–602
45. Fabre R, Merens A, Lefebvre F, Epifanoff G, Cerutti F, Pupin H, Tardif D, Cavallo JD, Ternois I (2010) Susceptibility to antibiotics of *Escherichia coli* isolated from community-acquired urinary tract infections. *Méd Mal Infect* 40:555–559
46. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA (2003) Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. *Cochrane Database Syst Rev*: CD003966
47. Oreskovic NM, Sembrano EU (2007) Repeat urine cultures in children who are admitted with urinary tract infections. *Pediatrics* 119:e325–e329
48. Currie ML, Mitz L, Raasch CS, Greenbaum LA (2003) Follow-up urine cultures and fever in children with urinary tract infection. *Arch Pediatr Adolesc Med* 157:1237–1240
49. Cheng CH, Tsai MH, Huang YC, Su LH, Tsau YK, Lin CJ, Chiu CH, Lin TY (2008) Antibiotic resistance patterns of community-acquired urinary tract infections in children with vesicoureteral reflux receiving prophylactic antibiotic therapy. *Pediatrics* 122:1212–1217
50. Williams GJ, Wei L, Lee A, Craig JC (2006) Long-term antibiotics for preventing recurrent urinary tract infection in children. *Cochrane Database Syst Rev* 3:CD001534
51. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L (2006) Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics* 117:626–632
52. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, Raymond F, Grellier A, Hazart I, de Parscau L, Salomon R, Champion G, Leroy V, Guignon V, Siret D, Palcoux JB, Taque S, Lemoigne A, Nguyen JM, Guyot C (2008) Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. *J Urol* 179:674–679, discussion 679
53. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, Minisini S, Ventura A (2008) Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics* 121:e1489–e1494
54. Montini G, Rigon L, Zucchetto P, Fregonese F, Toffolo A, Gobber D, Cecchin D, Pavanello L, Molinari PP, Maschio F, Zanchetta S, Cassar W, Casadio L, Crivellaro C, Fortunati P, Corsini A, Calderan A, Comacchio S, Tommasi L, Hewitt IK, Da Dalt L, Zacchello G, Dall'Amico R (2008) Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics* 122:1064–1071
55. Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, Hodson EM, Carapetis JR, Cranswick NE, Smith G, Irwig LM, Caldwell PH, Hamilton S, Roy LP (2009) Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med* 361:1748–1759
56. Brandstrom P, Esbjorner E, Herthelius M, Swerkersson S, Jodal U, Hansson S (2010) The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol* 184:286–291
57. Brandstrom P, Neveus T, Sixt R, Stokland E, Jodal U, Hansson S (2010) The Swedish reflux trial in children: IV. Renal damage. *J Urol* 184:292–297
58. Holmdahl G, Brandstrom P, Lackgren G, Sillen U, Stokland E, Jodal U, Hansson S (2010) The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. *J Urol* 184:280–285

Answers:

1. b. Urethral catheterization or suprapubic aspiration should be performed in infants and newborn
2. d. LE and nitrite
3. d. Can be a normal finding in children with neurogenic bladder
4. c. DMSA renal scan