Urinary tract infections in infants and children older than one month: Acute management, imaging, and prognosis

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INTRODUCTION — Urinary tract infections (UTI) are a common and important clinical problem in childhood. Upper urinary tract infections (ie, acute pyelonephritis) may lead to renal scarring, hypertension, and end-stage renal dysfunction. Although children with pyelonephritis tend to present with fever, it can be difficult on clinical grounds to distinguish cystitis from pyelonephritis, particularly in young children (those younger than two years) [1]. Thus, we have defined UTI broadly here without attempting to distinguish cystitis from pyelonephritis. Acute cystitis in older children is discussed separately. (See "Acute cystitis: Clinical features and diagnosis in children older than two years and adolescents".)

The acute management and prognosis of UTI in children will be reviewed here. The epidemiology, risk factors, clinical features, diagnosis, long-term management, and prevention of UTI in children and UTI in newborns are discussed separately. (See "Urinary tract infections in children: Epidemiology and risk factors" and "Urinary tract infections in infants and children older than one month: Clinical features and diagnosis" and "Urinary tract infections in children: Long-term management and prevention" and "Urinary tract infections in neonates".)

OVERVIEW

Goals — The goals of treatment for urinary tract infections (UTI) include [2,3]:

- Elimination of infection and prevention of urosepsis
- Prevention of recurrence and long-term complications including hypertension, renal scarring, and impaired renal growth and function
- Relief of acute symptoms (eg, fever, dysuria, frequency)

Acute management of UTI in children consists of antimicrobial therapy to treat the acute infection and evaluation for possible predisposing factors (eg, urologic abnormalities). Long-term management centers on prevention of recurrence and complications; it is discussed separately. (See "Urinary tract infections in children: Long-term management and prevention".)

Decision to hospitalize — Most infants older than two months with UTI can be safely managed as outpatients as long as close follow-up is possible [3-5].

Usual indications for hospitalization and/or parenteral therapy include [3,6-8]:

- Age <2 months
- Clinical urosepsis (eg, toxic appearance, hypotension, poor capillary refill)
- Immunocompromised patient
- Vomiting or inability to tolerate oral medication
- Lack of adequate outpatient follow-up (eg, no telephone, live far from hospital, etc)
- Failure to respond to outpatient therapy (see 'Response to therapy' below)

ANTIBIOTIC THERAPY — The effectiveness of antimicrobial therapy for urinary tract infections (UTI) is demonstrated by the change in mortality between the pre- and post-antibiotic eras. The mortality of UTI was as high

as 20 percent in the preantibiotic era. In contrast, when UTI are appropriately treated with antibiotics, acute complications (eg, renal abscess, death) are uncommon [9]. (See 'Prognosis' below.)

Antimicrobial therapy for children with presumed UTI depends upon a number of factors, including the age of the child, severity of illness, presence of vomiting, duration of fever before presentation, underlying medical and/or urologic problems, and the antimicrobial resistance patterns in the community.

Empiric therapy — Early and aggressive antibiotic therapy (eg, within 72 hours of presentation) is necessary to prevent renal damage. Delayed therapy has been associated with increased severity of infection and greater likelihood of renal damage in experimental, retrospective, prospective, and small randomized studies [10-17].

Decisions regarding the initiation of empiric antimicrobial therapy for UTI are best made on a case-by-case basis based upon the probability of UTI, which is determined by demographic and clinical factors [18].

We suggest that empiric antimicrobial therapy be initiated immediately after appropriate urine collection in children with suspected UTI and a positive urinalysis. This is particularly true for children who are at increased risk for renal scarring if UTI is not promptly treated, including children who present with:

- Fever (especially >39°C [102.2°F] or >48 hours)
- Ill appearance
- Costovertebral angle tenderness
- Known immune deficiency
- Known urologic abnormality

Choice of agent — A Gram-stained smear of the urine, if readily available, can help guide decisions regarding empiric therapy. The ultimate choice of antimicrobial therapy is based upon the susceptibilities of the organism isolated.

Escherichia coli is the most common bacterial cause of UTI; it accounts for approximately 80 percent of UTI in children [19]. Other gram-negative bacterial pathogens include *Klebsiella*, *Proteus*, *Enterobacter*, and *Citrobacter*. Gram-positive bacterial pathogens include *Staphylococcus saprophyticus*, *Enterococcus*, and, rarely, *Staphylococcus aureus*. (See "Urinary tract infections in children: Epidemiology and risk factors", section on 'Microbiology'.)

We recommend that empiric therapy for UTI in infants and children include an antibiotic that provides adequate coverage for *E. coli*. The agent of choice should be guided by local resistance patterns.

Approximately 50 percent of *E. coli* are resistant to amoxicillin or ampicillin [20-23]. In addition, increasing rates of *E. coli* resistance to first-generation cephalosporins (eg, cephalexin), amoxicillin-clavulanate or ampicillin-sulbactam, and trimethoprim-sulfamethoxazole (TMP-SMX) have been reported in some communities [19-27]. Increased resistance to extended-spectrum cephalosporins (cefotaxime, ceftazidime, cefepime), has been reported in children receiving prophylactic antibiotics [28-30]. (See 'Recent antibiotic exposure' below.)

Third-generation cephalosporins (eg, cefpodoxime, cefixime, cefdinir, ceftibuten, cefotaxime, ceftriaxone) and aminoglycosides (eg, gentamicin, amikacin) are appropriate first-line agents for empiric treatment of UTI in children. However, these drugs are not effective in treating *Enterococcus* and should not be used as monotherapy for patients in whom enterococcal UTI is suspected (eg, those with a urinary catheter in place, instrumentation of the urinary tract, or an anatomical abnormality). In such patients, amoxicillin or ampicillin should be added. Hydration status and renal function should be assessed in patients who are treated with aminoglycosides.

Oral therapy — Most children older than two months of age who are not vomiting can be treated with orally administered antimicrobials [3,31]. Close contact with the family should be maintained for the first two to three days of therapy; the seriousness of the infection and the need for completion of the entire course of therapy should be stressed.

We suggest a third-generation cephalosporin (eg, cefixime cefdinir, ceftibuten) as the first-line oral agent in the treatment of UTI in children without genitourinary abnormalities [4,5,32,33]. In a randomized, controlled trial of 306 children 1 to 24 months of age with a febrile UTI, oral therapy with cefixime for 14 days was as effective as intravenous therapy with cefotaxime for three days followed by oral therapy with cefixime [4]. The rates of symptom resolution (mean time to defervescence approximately 24 hours), sterilization of the urine (100 percent), reinfection (4.6 and 7.2 percent), and renal scarring at six months (9.8 and 7.2 percent) did not differ between groups.

A similar trial in children 6 months to 16 years, albeit limited by imbalances in treatment group comparability at baseline and high drop-out rates, found once-daily therapy with ceftibuten to be comparable to initial therapy with ceftriaxone followed by ceftibuten [32]. Oral amoxicillin-clavulanate (50 mg/kg per day in three divided doses) also was shown to be as effective as parenteral therapy followed by oral therapy in a multicenter, randomized trial [34]. However, amoxicillin-clavulanate is associated with increasing rates of resistance. In a child with a penicillin and cephalosporin allergy, treatment with trimethoprim-sulfamethoxazole (TMP-SMX), or ciprofloxacin (if the local resistance rates to TMP-SMX are known to be high) and close follow-up of the antimicrobial sensitivity results is a reasonable strategy.

Cefixime, cefdinir, and ceftibuten are dosed as follows:

- Cefixime (16 mg/kg by mouth on the first day, followed by 8 mg/kg once daily to complete therapy) (see 'Duration of therapy' below)
- Cefdinir (14 mg/kg by mouth once daily)
- Ceftibuten (9 mg/kg by mouth once daily)

Other third-generation cephalosporins that may be used for oral therapy include cefpodoxime (10 mg/kg once daily) [3]. However, no large trials have specifically examined the efficacy of these agents for pediatric UTI.

Amoxicillin and ampicillin are not routinely recommended for empiric therapy because of the high rate of resistance of *E. coli*. Similarly, amoxicillin-clavulanate, first-generation cephalosporins (eg, cephalexin), and TMP-SMX should be used with caution because of the increasing rates of resistance to these drugs in some communities [19-27].

Fluoroquinolones (eg, ciprofloxacin) are effective for *E. coli*, and resistance is rare. However, the safety of quinolones in children is still under study [35]. In addition, the widespread use of fluoroquinolones is leading to increased resistance among other bacteria [36-38]. Ciprofloxacin should not be used as a first-line agent. The American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommends that the use of ciprofloxacin for UTI in children be limited to UTI caused by *Pseudomonas aeruginosa* or other multidrug-resistant, gram-negative bacteria [35].

Oral agents that are excreted in the urine but do not achieve therapeutic serum concentrations (eg, nalidixic acid, nitrofurantoin) should not be used to treat UTI in febrile infants and young children in whom renal involvement is likely because parenchymal and serum concentrations may be insufficient to treat pyelonephritis or urosepsis [3].

Parenteral therapy — Third- or fourth-generation cephalosporins (eg, cefotaxime, ceftriaxone, cefepime) and aminoglycosides (eg, gentamicin) are appropriate first-line parenteral agents for empiric treatment of UTI in children. Definitive therapy is based upon the results of urine culture and sensitivities.

Acceptable inpatient treatment regimens include the combination of ampicillin and gentamicin; gentamicin alone; or a third- or fourth-generation cephalosporin [9,39,40]. Ampicillin should be included if enterococcal UTI is suspected. (See 'Recent antibiotic exposure' below.)

The doses are as follows [3,41]:

- Ampicillin (100 mg/kg/day IV divided in four doses)
- Gentamicin (7.5 mg/kg/day IV divided in three doses)

- Cefotaxime (150 mg/kg per day IV divided in three or four doses)
- Ceftriaxone (50 to 75 mg/kg per day IV)
- Cefepime (100 mg/kg per day divided in two doses for children weighing ≤40 kg, maximum daily dose 1 g; 500 mg twice per day for children weighing >40 kg)

Parenteral antibiotics should be continued until the patient is clinically improved (eg, afebrile) and able to tolerate oral liquids and medications [3].

Outpatient parenteral therapy — Once-daily parenteral administration of gentamicin or ceftriaxone in a day treatment center may avoid the need for hospital admission in select patients (eg, children who are ≥3 months old who are unable to tolerate oral therapy and are nontoxic appearing, well hydrated, without urologic abnormalities, and whose caretakers will be able to adhere to the outpatient regimen) [42-44].

Recent antibiotic exposure — Recent exposure to antibiotics, whether for treatment of an infection or as antimicrobial prophylaxis, is an important consideration in the choice of empiric antibiotic therapy [28-30,45,46].

Recurrent UTI — Review of the antimicrobial susceptibilities of the most recent urinary pathogens can be helpful in choosing empiric therapy for children with recurrent UTI.

Duration of therapy — In a systematic review, short course antimicrobial therapy (two to four days) was as effective as standard duration (7 to 14 days) therapy in eradicating bacteria in children with suspected lower urinary tract infection (ie, afebrile children) [47]. However, little evidence is available to guide duration of antimicrobial therapy in children with febrile UTIs. A multicenter trial, sponsored by the National Institutes of Health, is being conducted to determine the efficacy of short-course therapy for UTI in children. If efficacious, short-course therapy may enable clinicians to limit the duration of exposure to antimicrobials to that needed to eradicate the offending uropathogen, reducing the likelihood of adverse events and the emergence of bacterial resistance.

In the meantime, we suggest a longer course of therapy for febrile children (usually 10 days) and a short course of therapy (three to five days) for immune competent children presenting without fever.

Response to therapy

Clinical response — The clinical condition of most patients improves within 24 to 48 hours of initiation of appropriate antimicrobial therapy [48].

The mean time to resolution of fever is 24 hours, but fever may persist beyond 48 hours [4]. In a review of 288 children younger than two years who were admitted to a tertiary-care children's hospital with febrile UTI, 89 percent were afebrile within 48 hours of antimicrobial therapy [48]. No differences were noted between those who remained febrile >48 hours and those who were afebrile within 48 hours with respect to bacteremia (42 and 35 percent, respectively), hydronephrosis (3 and 8 percent, respectively) and significant vesicoureteral reflux (VUR) (19 and 14 percent, respectively).

In children whose clinical condition (other than persistent fever) worsens or fails to improve as expected within 48 hours of initiation of antimicrobial therapy, broadening antimicrobial therapy may be indicated if the culture and sensitivity results are not yet available. Most of the empiric regimens suggested above do not provide adequate coverage for *Enterococcus*.

In addition, in children who worsen or fail to improve within 48 hours, renal and bladder ultrasonography (RBUS) should be performed as soon as possible (to evaluate the presence of a renal abscess or surgically correctable anatomic abnormalities or obstruction) [3,49,50]. (See 'Imaging' below.)

Repeat urine culture — Several observational studies suggest there is little utility in repeating the urine culture in children with UTI who are treated with an antibiotic to which their uropathogen is susceptible [48,51,52].

Accordingly, it is not necessary to routinely obtain repeat urine cultures during antimicrobial therapy to document

sterilization of the urine, provided that the child has had the expected clinical response and the uropathogen is susceptible to the antibiotic that is used for treatment [48,51-53]. However, urine cultures should be performed after 48 hours of therapy if the patient fails to respond clinically or if the uropathogen is not susceptible (intermediate or resistant) to the antibiotic that is being used for treatment. It is important to routinely perform susceptibility testing on the isolated uropathogens to avoid unnecessary delay in administration of appropriate therapy.

Prophylactic antibiotics — Decisions regarding prophylactic antibiotics for children following initial febrile UTI should be made on a case-by-case basis.

- Antibiotic prophylaxis for children who have undergone VCUG and have documented VUR (of any grade) is discussed separately (see 'Voiding cystourethrogram' below and "Management of vesicoureteral reflux")
- For children who have undergone VCUG and do not have VUR or other renal/urologic abnormalities, we generally do not suggest prophylactic antibiotics after the first febrile UTI
- For children with a first febrile UTI and for whom a decision is made to defer VCUG pending recurrence (but who may have VUR), factors to consider include (see 'Voiding cystourethrogram' below):
    - The decreased risk of febrile or symptomatic UTI recurrence in children with VUR, particularly in those with bowel and bladder dysfunction, and febrile first UTI [54]
    - Family history of VUR, which increases the risk of VUR (see "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux", section on 'Genetics')
    - Age, sex, and race/ethnicity, all of which affect the probability of VUR (increased in children <2 years, girls, and white versus black children) (see "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux", section on 'Epidemiology')
    - Severity of the UTI
    - The importance the parents place on prevention of recurrence (which may result in alarming symptoms, hospitalization, and loss of work)
    - Ability to adhere to prophylaxis
    - Parental concern about development of antimicrobial resistance and potential impact on the microbiome

Whether administration of prophylactic antibiotics after initial febrile UTI prevents recurrent urinary tract infection or renal scarring in children (with and without VUR) has been controversial. Randomized trials evaluating this question have had inconsistent results [55-60]. A meta-analysis of individual data in infants and young children (2 to 24 months) without VUR and with VUR of grades I to IV did not detect a benefit for prophylaxis in preventing recurrence [3]. However, some of the included trials had methodologic problems potentially biasing results toward no effect (eg, insufficient power; lack of blinding; non-stringent diagnostic criteria; inclusion of uncircumcised boys, which limits generalizability to populations where most boys are circumcised; and misclassification of asymptomatic bacteriuria as recurrent UTIs) [61].

Two large, well-designed trials, one included in the meta-analysis [56], and one published subsequently (the Randomized Intervention for Vesicoureteral Reflux [RIVUR] trial) [54], demonstrate that antimicrobial prophylaxis prevents recurrent UTI in children with VUR. The RIVUR trial evaluated the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis 3 mg/kg of trimethoprim plus 15 mg/kg of sulfamethoxazole daily in preventing febrile or symptomatic urinary tract infection recurrences (primary outcome) in 607 children (two months to six years) who were diagnosed with grade I to IV VUR after a first or second febrile or symptomatic UTI and were followed for two years. Renal scarring, treatment failure (a composite of recurrences and scarring), and antimicrobial resistance were secondary outcomes. Key findings were as follows:

- Fewer children who received TMP-SMX had recurrent febrile or symptomatic UTI (13 versus 25 percent), reducing the risk of recurrent febrile or symptomatic UTI by 50 percent (hazard ratio [HR], 0.50, 95% CI 0.34-

0.74).

In subgroup analysis, antibiotic prophylaxis was most effective in children with bowel and bladder dysfunction (hazard ratio 0.21, 95% CI 0.08-0.58) and children whose first UTI was febrile (HR 0.41, 95% CI 0.26-0.64).

- TMP-SMX prophylaxis did not reduce the incidence of renal scarring (11.9 and 10.2 percent), severe renal scars (4.0 and 2.6 percent), or new renal scars (8.2 and 8.4 percent), as assessed by renal scintigraphy at baseline, one-year follow-up, and two-year follow-up.
- Compared to children in the placebo group, children treated with TMP-SMX who had a first recurrent *E. coli* UTI infection during the follow-up period had increased risk of TMP-SMX resistance (63 versus 19 percent).

The 2011 AAP practice guideline does not recommend prophylactic antimicrobials following the first febrile UTI in children 2 to 24 months [3]. The United Kingdom's National Institute for Health and Care Excellence (NICE) guideline for UTI in children indicates that antibiotic prophylaxis should not be routinely recommended in infants and children following their first UTI, but may be warranted after recurrent UTI [53]. (See "Urinary tract infections in children: Long-term management and prevention", section on 'Prophylaxis'.)

ADJUNCTIVE THERAPIES — Renal parenchymal inflammation during urinary tract infections (UTI) may lead to renal scarring, although the predisposing factors are not well understood [62]. The role of renal parenchymal inflammation in the development of renal scars, and the potential role of anti-inflammatory agents in preventing renal scars has been evaluated in several studies [63-65]. An observational study demonstrated that dexamethasone decreased urinary levels of interleukin-6 and interleukin-8 in children, suggesting a possible role for glucocorticoids in the prevention of scar formation [64]. This hypothesis was supported by a trial in which 84 children <16 years with first episode of acute pyelonephritis and high risk of renal scar formation were randomly assigned to receive oral methylprednisolone or placebo in addition to antibiotic therapy (19 in the methylprednisolone group and 65 in the placebo group) [65]. Treatment with methylprednisolone was associated with decreased renal scarring at six months (33 versus 60 percent in the methylprednisolone and placebo groups, respectively) without significant adverse effects, relapse, or recurrence.

Results of this small study are difficult to generalize because enrollment required 1) performance of a renal scintigram within 48 hours of diagnosis, which was not conducted in all patients, and 2) severe renal involvement in children who were all hospitalized. Additional studies are necessary to confirm these results and to determine the optimum glucocorticoid regimen before adjunctive glucocorticoids are routinely recommended in the treatment of UTI in children. A large randomized trial sponsored by the National Institutes of Health is being conducted to answer these questions [66].

IMAGING

Rationale — The rationale for imaging in young children with urinary tract infections (UTI) is to identify abnormalities of the genitourinary tract that require additional evaluation or management (eg, obstructive uropathies, dilating vesicoureteral reflux [VUR]). If such abnormalities are detected, steps can be taken to modify the risk of subsequent renal damage (eg, surgical intervention or antibiotic prophylaxis to prevent recurrent UTI).

The ultimate value of detecting anatomic or functional abnormalities of the urinary tract depends upon the effectiveness of the interventions designed to prevent recurrent UTI and renal scarring [67,68]. Evidence to support the utility of routine imaging in reducing long-term sequelae (renal scarring, hypertension, renal failure) is limited [69-73], and there is a lack of consensus about the optimal imaging strategy [3,53,74-76].

Ultrasonography — Renal and bladder ultrasonography (RBUS) is a non-invasive test that can demonstrate the size and shape of the kidneys, the presence of duplication and dilatation of the ureters, and the existence of gross anatomic abnormalities. RBUS can also identify renal or perirenal abscess or pyonephrosis in children with acute UTI who fail to improve with antimicrobial therapy. Although RBUS is not reliable in diagnosing renal scarring or VUR [77,78], abnormalities on RBUS after first UTI are useful in predicting the risk of renal scarring [73]. (See "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux".)

RBUS is estimated to yield management-altering abnormalities (ie, requiring additional evaluation or surgery) in only 1 to 2 percent of cases of first febrile UTI in young children 2 to 24 months of age [1,3,55,79,80]. The false positive rate is between 2 and 3 percent [3]. The major advantages of RBUS are the lack of exposure to radiation and helpfulness in predicting risk of renal scarring [73].

Indications — Given the potentially large benefit of detecting correctible malformations for a small number of children and the low risk of harm, we suggest RBUS for the following children:

- Children younger than two years of age with a first febrile UTI
- Children of any age with recurrent febrile UTIs
- Children of any age with a UTI who have a family history of renal or urologic disease, poor growth, or hypertension (calculator 1 and calculator 2)
- Children who do not respond as expected to appropriate antimicrobial therapy

However, many women have prenatal ultrasonography after 30 to 32 weeks of gestation—a time at which the urinary tract is fully developed; we may elect not to perform RBUS (in children of any age) if prenatal ultrasonography that was performed at a reputable center was normal and the study results are accessible [81,82].

The American Academy of Pediatrics (AAP) recommends RBUS for all infants and children 2 to 24 months following their first febrile UTI [3]. The United Kingdom's National Institute for Health and Care Excellence (NICE) guideline on UTI in children recommends RBUS for infants younger than six months and for children older than six months who have atypical or recurrent UTI [53]. They define atypical UTI as serious illness, poor urine flow, abdominal or bladder mass; elevated creatinine, septicemia, infection with an organism other than *E. coli*, and failure to respond to antibiotics within 48 hours; they define recurrence as ≥2 episodes of upper UTI, one episode of upper UTI plus ≥1 episode of lower UTI, or ≥3 episodes of lower UTI.

Timing — When the RBUS should be performed depends upon the clinical situation [3]. In infants and young children with unusually severe illness or failure to improve as expected after initiation of antimicrobial therapy, RBUS should be performed as soon as possible during the acute phase of illness to identify complications (eg, renal or perirenal abscess, pyonephrosis). However, for infants and young children who respond as expected to appropriate antimicrobial therapy, RBUS should be performed after the acute phase (to reduce the risk of false positive results secondary to renal inflammation during the acute episode) [3,53]. The decision to treat with prophylactic antibiotics pending results of imaging is discussed above. (See 'Prophylactic antibiotics' above.)

Voiding cystourethrogram — The voiding cystourethrogram (VCUG) is the test of choice to establish the presence and degree of vesicoureteral reflux (VUR). VUR is the retrograde passage of urine from the bladder into the upper urinary tract. It is an important risk factor for renal scarring. Approximately 25 to 30 percent of children (0 to 18 years) with a first UTI have VUR [68,73]. (See 'Prognosis' below and "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux" and "Urinary tract infections in children: Epidemiology and risk factors", section on 'Risk factors for renal scarring'.)

VCUG involves catheterization to fill the bladder with a radiopaque or radioactive liquid and recording of VUR during voiding. VCUG is expensive, invasive, and may miss a significant portion of children who are at risk for renal scarring [68]. The radiation exposure depends upon the technique and equipment used (the pediatric effective dose estimate ranges from 0.03 to 0.3 mSV) [83]. (See "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux", section on 'Diagnosis' and "Radiation-related risks of imaging studies".)

Indications — Decisions about performing a VCUG in infants and children with UTI must take into consideration the factors described above, namely likelihood of VUR, severity of UTI, importance parents place in preventing recurrences, cost and discomfort of the VCUG, perceived likelihood of adherence to prophylaxis, and concerns about resistance. (See 'Prophylactic antibiotics' above.)

Pending results of ongoing cost-effectiveness analysis of the Randomized Intervention for Vesicoureteral Reflux

(RIVUR) data, we suggest performance of a VCUG to diagnose VUR in:

- Children of any age with two or more febrile UTIs, **or**
- Children of any age with a first febrile UTI **and**:
  - Any anomalies on renal ultrasound, **or**
  - The combination of temperature ≥39°C (102.2°F) and a pathogen other than *E. coli*, **or**
  - Poor growth or hypertension (calculator 1 and calculator 2).

In a meta-analysis of individual patient data from nine studies including 1280 children (0 to 18 years) with initial UTI, 68 percent of children with grade IV or V VUR had either abnormal RBUS or the combination of temperature ≥39°C (102.2°F) and a pathogen other than *E. coli* [73]. (See "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux" and "Management of vesicoureteral reflux".)

For children with a first febrile UTI and **without** abnormalities on renal ultrasonography, the combination of temperature ≥39°C (102.2°F) and a pathogen other than E. coli, poor growth, or hypertension, a strategy of "watchful waiting" (ie, observation and performance of VCUG with recurrence) seems reasonable [84], particularly if the family would prefer to avoid prophylactic antibiotics. These children are less likely to have VUR and VCUG results are less likely to affect management.

It remains uncertain whether the benefits of detection and treatment of VUR after the first UTI outweigh the risks. The uncertainty centers on the changing view of the role of VUR in the development of renal damage and progressive kidney disease and the lack of clarity regarding the effectiveness of medical or surgical management of VUR in reducing the risk of renal scarring [68]. Although the risk of renal scarring is increased in children with VUR compared with children without VUR (41 versus 17 percent in a systematic review) and increases with increasing grades of VUR, VUR is neither necessary nor sufficient for the development of renal scars [68,73]. (See "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux", section on 'Renal scarring and/or dysplasia'.)

Early trials comparing antireflux surgery with antimicrobial prophylaxis in children with VUR showed no differences in rates of recurrent UTI or renal scarring [85-88], but the lack of a placebo or observation group precluded determination that either treatment was more effective than no treatment [85-88]. Subsequent randomized trials comparing antimicrobial prophylaxis with no treatment or placebo had inconsistent results regarding recurrence of UTI, but most of these trials were not blinded [55-59,61]. (See "Management of vesicoureteral reflux", section on 'Choice of therapy'.)

The RIVUR trial addressed many of these issues. It evaluated the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis in preventing febrile or symptomatic urinary tract infection recurrences (primary outcome) in 607 children (two months to six years) who were diagnosed with grade I to IV VUR after a first or second febrile or symptomatic UTI and were followed for two years [54]. Renal scarring, treatment failure (a composite of recurrences and scarring), and antimicrobial resistance were secondary outcomes. The RIVUR trial demonstrated unequivocally that prophylactic antibiotics decrease the risk of febrile, recurrent UTI (HR 0.50, 95% CI 0.34 to 0.74) [54]. Nearly twice as many children receiving placebo than children receiving prophylaxis were categorized as treatment failures (defined by two febrile UTIs, one febrile UTI and three symptomatic UTIs, four symptomatic UTIs, or new or worsening renal scarring). However, antibiotic prophylaxis did not reduce the risk of scarring, and was associated with antimicrobial resistance. (See 'Prophylactic antibiotics' above.)

The 2011 AAP clinical practice guideline recommends postponing VCUG until the second febrile UTI in children 2 to 24 months of age unless there are atypical or complex clinical circumstances or the RBUS reveals hydronephrosis, scarring, or other findings suggestive of high-grade (IV or V) VUR or obstructive uropathy [3]. The recommendation was reaffirmed after publication of the results of the RIVUR trial [89]. According to the guideline, the benefit of avoiding radiation exposure and discomfort in the majority of patients outweighs delayed detection of a small number of cases of high-grade reflux or surgically correctible abnormalities. However, the guideline acknowledges that parent preferences may play a role in the decision to perform VCUG.

The United Kingdom's NICE guideline suggests VCUG for infants <6 months with atypical or recurrent UTI [53]. They define atypical UTI as serious illness, poor urine flow, abdominal or bladder mass; elevated creatinine, septicemia, infection with an organism other than *E. coli*, and failure to respond to antibiotics within 48 hours; they define recurrence as ≥2 episodes of upper UTI, one episode of upper UTI plus ≥1 episode of lower UTI, or ≥3 episodes of lower UTI. The NICE guidelines also suggest that VCUG may be warranted for children six months to three years with atypical or recurrent UTI and dilation on ultrasonography, poor urine flow, non-*E. coli* infection, or family history of VUR. They define atypical UTI as serious illness, poor urine flow, abdominal or bladder mass; elevated creatinine, septicemia, infection with an organism other than *E. coli*, and failure to respond to antibiotics within 48 hours; they define recurrence as ≥2 episodes of upper UTI, one episode of upper UTI plus ≥1 episode of lower UTI, or ≥3 episodes of lower UTI.

Timing — Although VCUG is often scheduled several weeks after UTI, it may be performed as soon as the patient is asymptomatic [90]. Early imaging (as early as the first week) does not appear to falsely increase the detection of VUR [91-94]. To avoid the use of prophylactic antibiotics in children without VUR, we prefer to conduct VCUGs during the last days of antimicrobial therapy or immediately after completion of antimicrobial therapy for UTI.

Renal scintigraphy — Renal scintigraphy using dimercaptosuccinic acid (DMSA) can be used to detect acute pyelonephritis and renal scarring in the acute and chronic settings, respectively [1,3,95]. DMSA is injected intravenously, and uptake by the kidney is measured two to four hours later. Areas of decreased uptake represent pyelonephritis or scarring. DMSA scans are expensive, invasive, and expose children to radiation (the pediatric effective dose estimate ranges from 0.3 to 3 mSV) [83]. (See "Radiation-related risks of imaging studies".)

The role of renal scintigraphy in the management of children with acute UTI is controversial. Scintigraphy at the time of an acute UTI provides information about the extent of renal parenchymal involvement. In addition, DMSA will identify most (>70 percent) children with moderate to severe VUR (grade III or higher) [96-98]. This observation has prompted some experts to suggest that DMSA be used as the initial imaging test to identify children at higher risk for renal scarring (the "top down" approach) [99].

However, using DMSA as the initial test to identify high-risk children is more expensive, and involves greater exposure to radiation [100]. Furthermore, since most young febrile children with UTI have pyelonephritis and a positive DMSA, this strategy may lead to identification of a large number of children who may or may not be at risk for future UTI [1,68]. In a systematic review of 33 studies, approximately 60 percent of children with initial UTI had DMSA scans consistent with acute pyelonephritis in the acute phase of illness, but only 15 percent had renal scarring at follow-up [68]. It is unclear how to best manage children with positive acute-phase DMSA scan. Careful clinical follow-up of all children with UTI may obviate the need for routine DMSA. (See 'Follow-up' below.)

We suggest not using DMSA in the routine evaluation of children with first UTI. This is consistent with the AAP and NICE guidelines [3,53].

Some experts recommend DMSA 6 to 12 months after acute infection to detect the formation of scarring which would require follow-up [101,102]. The NICE guidelines recommend DMSA four to six months after acute infection for children younger than three years with atypical or recurrent UTI and for children older than three years with recurrent UTI [53]. They define atypical UTI as serious illness, poor urine flow, abdominal or bladder mass; elevated creatinine, septicemia, infection with an organism other than *E. coli*, and failure to respond to antibiotics within 48 hours; they define recurrence as ≥2 episodes of upper UTI, one episode of upper UTI plus ≥1 episode of lower UTI, or ≥3 episodes of lower UTI.

FOLLOW-UP — Recurrent urinary tract infection (UTI) is a risk factor for renal scarring. Parents of infants and young children who have been treated for a febrile UTI and children with bowel and bladder dysfunction (a risk factor for recurrent UTI) should be instructed to seek prompt evaluation for subsequent febrile illnesses to ensure prompt recognition and treatment of recurrent UTI [3,53,61]. The evaluation of these episodes should include urinalysis and urine culture [1]. Among children younger than six years, the risk of recurrence appears to be increased in those who are white (hazard ratio [HR], 2.0), age three to five years (HR ~2.5), and those with grade IV to V VUR (HR

4.38) [45].

Prompt diagnosis and effective treatment of recurrent febrile UTI and treatment of bowel and bladder dysfunction that predisposes many children to UTI may be more important than identifying anatomic or functional genitourinary abnormalities after the first febrile UTI in preventing renal scarring [3]. The risk of renal scarring increases with recurrent episodes of pyelonephritis, from approximately 5 percent after the first episode to 10 percent after the second, 20 percent after the third, 40 percent after the fourth, and 60 percent after the fifth [103].

Primary care follow-up for infants and young children who have had a febrile UTI should include regular monitoring of height, weight, and blood pressure. (See "Clinical presentation and evaluation of chronic kidney disease in children", section on 'Clinical presentation'.)

INDICATIONS FOR REFERRAL — Potential indications for referral to a nephrologist or urologist with expertise in children include [53]:

- Dilating vesicoureteral reflux (Grades III to V) or obstructive uropathy
- Renal abnormalities
- Impaired kidney function
- Elevated blood pressure
- Bowel and bladder dysfunction refractory to primary care measures (see "Urinary tract infections in children: Long-term management and prevention", section on 'Children with bowel and bladder dysfunction')

PROGNOSIS — The short-term outcome of first urinary tract infection (UTI) in children (<19 years) was described in a systematic review of 33 studies, including 4891 children [68]:

- Twenty-five percent had vesicoureteral reflux (VUR); 2.5 percent had grade IV or V VUR
- VUR was associated with an increased risk of developing acute pyelonephritis (relative risk [RR] 1.5, 95% CI 1.1-1.9) and renal scarring (RR 2.6, 95% CI 1.7-3.9); grade III VUR was associated with increased risk of renal scarring compared with lower grades (RR 2.1, 95% CI 1.4-3.2)
- Fifteen percent (95% CI 11-18 percent) of children had evidence of renal scarring on follow-up dimercaptosuccinic acid (DMSA) scan (5 to 24 months later); the long-term significance of scarring, as identified by DMSA, remains to be determined
- Eight percent (95% CI 5-11 percent) of children had at least one recurrence

Risk factors for recurrence among children younger than six years include white race (hazard ratio [HR], 2.0), age three to five years (HR ~2.5), and grade IV to V VUR (HR 4.38) [45].

Predicting which children with UTI will develop long-term sequelae remains difficult. A systematic review of the literature found only four prospective, relatively small studies addressing this question [104]. The large majority of children with UTI have no long-term sequelae, as illustrated by the following studies:

- In a study of 111 high-risk girls who were followed for 6 to 32 years after their initial UTI, only seven (6 percent) had decreased glomerular filtration rate (GFR), and none developed chronic kidney disease [105].
- In another study of 68 children with history of urographic renal scarring who were followed for 16 to 26 years after their index UTI, median GFR [69] and mean 24-hour ambulatory blood pressure [106] were no different in children with and without urographic renal scarring. No child developed chronic kidney disease.
- In a study of 226 children with UTI followed for one to 41 years, two developed chronic kidney disease that appeared to be attributable to the UTIs [107].

The prognosis for children with nonfebrile UTI is discussed separately. (See "Acute cystitis: Management and prognosis in children older than two years and adolescents", section on 'Prognosis'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: Urinary tract infections in children (The Basics)")
- Beyond the Basics topic (see "Patient information: Urinary tract infections in children (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Most children with urinary tract infection (UTI) can be managed as outpatients. Indications for hospitalization may include age <2 months, clinical urosepsis, immunocompromised patient, vomiting or inability to tolerate oral medication, lack of outpatient follow-up, and failure to respond to outpatient therapy. (See 'Decision to hospitalize' above.)
- Empiric antimicrobial therapy immediately after appropriate urine collection is warranted in children with suspected UTI and a positive urinalysis. This is particularly true for young children with fever (especially if >39°C [102.2°F] or >48 hours), ill appearance, costovertebral angle tenderness, known immune deficiency, or known urologic abnormality. (See 'Empiric therapy' above.)
- We recommend that empiric therapy for UTI in children include an antibiotic that provides adequate coverage for *Escherichia coli* (**Grade 1B**). The agent of choice should be guided by local resistance patterns. Definitive therapy is based upon the results of urine culture and sensitivities. (See 'Choice of agent' above.)
    - We suggest a third-generation cephalosporin (eg, cefixime, cefdinir, ceftibuten) as the first-line oral agent in the treatment of UTI in children without genitourinary abnormalities (**Grade 2A**). Amoxicillin or ampicillin should be added if enterococcal infection is suspected. (See 'Oral therapy' above.)
    - Third- or fourth-generation cephalosporins (eg, cefotaxime, ceftriaxone, cefepime) and aminoglycosides (eg, gentamicin) are appropriate first-line parenteral agents for empiric treatment of UTI in children. (See 'Parenteral therapy' above.)
- The duration of therapy depends upon the age of the child and the clinical scenario. (See 'Duration of therapy' above.)
    - Febrile children are usually treated for 10 days
    - Afebrile children are usually treated for shorter periods (3 to 5 days) (see 'Duration of therapy' above and "Acute cystitis: Clinical features and diagnosis in children older than two years and adolescents")
- The clinical condition of most patients improves within 24 to 48 hours of initiation of appropriate antimicrobial therapy. (See 'Clinical response' above.)
- In children whose clinical condition worsens or fails to improve as expected within 24 to 48 hours of initiation of antimicrobial therapy, broadening of empiric therapy may be indicated. Renal bladder ultrasonography (RBUS) should be performed as soon as possible to evaluate the presence of renal abscess or surgically correctable anatomic abnormalities or obstruction. (See 'Clinical response' above.)
- We obtain routine RBUS after first febrile UTI in children younger than two years who did not have normal

prenatal ultrasonography at a reputable center at >30 to 32 weeks of gestation. We also obtain RBUS for children of any age with recurrent febrile UTIs and children of any age with a first UTI who have poor growth, hypertension, or a family history of renal or urologic disease. (See 'Ultrasonography' above.)

- We obtain voiding cystourethrogram (VCUG) to diagnose vesicoureteral reflux (VUR) in:
  - Children of any age with ≥2 febrile UTIs, or
  - Children of any age with a first febrile UTI and:
    - Any anomalies on renal ultrasound, **or**
    - The combination of temperature ≥39°C (102.2°F) and a pathogen other than *E. coli*, **or**
    - Poor growth or hypertension. (See 'Voiding cystourethrogram' above.)
- The majority of children with UTI have no long-term sequelae. Prediction of long-term sequelae in children with UTI remains difficult. (See 'Prognosis' above.)

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