Children’s UTIs in the new millennium

Diagnosis, investigation, and treatment of childhood urinary tract infections in the year 2001

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ABSTRACT

OBJECTIVE To provide an effective approach for family physicians treating children presenting with urinary tract infections (UTIs).

QUALITY OF EVIDENCE The information presented, and articles quoted, are drawn from both review of the literature and recent consensus guidelines. Data and recommendations come from prospective multicentre trials; retrospective reviews; expert consensus statements; and some smaller trials, commentaries, and editorials.

MAIN MESSAGE Urinary tract infections are often seen in family practice. Diagnosis requires suspicion and a realization that children, especially those younger than 2 years, often have very few, nonspecific signs of infection. Obtaining a proper urine sample is vital, because true infections require radiographic studies. Antibiotic prophylaxis is promoted because of the link between vesicoureteral reflux, recurrent UTIs, and renal scarring and hypertension. We generally provide prophylaxis until children are 3 or 4 years, when risk of damage from reflux is lessened and timely urine samples are easier to obtain for prompt therapy. Surgical opinion is sought only when medical management has failed. Failure is defined as either recurrent infections and pyelonephritis or poor renal growth.

CONCLUSION To diagnose UTIs in children, physicians must suspect them, obtain proper urine samples, order appropriate investigations to rule out underlying anatomic abnormalities, and treat with appropriate antibiotics considering both organism sensitivities and length of therapy.

RÉSUMÉ

OBJECTIF Présenter aux médecins de famille une approche thérapeutique efficace pour les enfants souffrant d’infections des voies urinaires (IVU).

QUALITÉ DES DONNÉES Les renseignements donnés et les articles cités proviennent à la fois d’une analyse des ouvrages scientifiques et des récents guides de pratique consensuels. Les données et les recommandations se fondent sur des essais prospectifs multicentriques, des déclarations consensuelles d’experts, ainsi que sur des essais de moins grande envergure, des commentaires et des éditoriaux.

PRINCIPAL MESSAGE Il est fréquent de rencontrer des infections des voies urinaires en pratique familiale. Dans le diagnostic, il faut suspecter et se rendre compte que les enfants, surtout ceux de moins de deux ans, présentent souvent des signes d’infection non spécifiques et plutôt rares. Il est essentiel d’obtenir un spécimen d’urine approprié car les infections véritables nécessitent des examens radiographiques. La prophylaxie aux antibiotiques est préconisée en raison du lien entre le reflux anormal d’urine vésicale vers les uretères, les IVU récurrentes, la cicatrisation rénale et l’hypertension. Nous prescrivons habituellement la prophylaxie aux enfants jusqu’à l’âge de trois ou quatre ans, lorsque le risque de dommages causés par le reflux est moins grand et qu’il est plus aisé d’obtenir des échantillons d’urine opportuns aux fins de thérapie immédiate. L’opinion d’un chirurgien n’est sollicitée que si le traitement médical échoue. L’échec se définit par des infections récurrentes et une pyélonéphrite ou une faible croissance rénale.

CONCLUSION Le diagnostic des IVU chez l’enfant exige du médecin qu’il les suspecte, obtienne un spécimen d’urine approprié, prescrive les investigations voulues pour exclure des anomalies physiques sous-jacentes et procède au traitement au moyen d’antibiotiques pertinents, compte tenu des sensibilités de l’organisme et de la durée de la thérapie.

This article has been peer reviewed.

Cet article a fait l’objet d’une évaluation externe.

his article aims to provide family physicians with an effective and reasonable approach to children who have, or are suspected to have, urinary tract infections (UTIs). This is an important topic for family physicians because it is a common problem in children. Hellstrom and associates\(^1\) showed, in children up to 7 years, a prevalence of culture-proven UTIs of 1.6% in boys and 7.8% in girls. This prevalence ensures that family physicians seeing young children in their practices will encounter this problem.

Young children, who have the highest incidence of infection, are the most difficult to assess. They require a comprehensive and reasonable approach to diagnosis, as well as effective treatments and timely investigations.

We hope this review will provide physicians with an approach they can apply to their particular needs and can use to evaluate and follow up children with UTIs. The take-home message is summarized by the rules in boldface placed throughout the paper (Table 1).

### Quality of evidence

MEDLINE was searched from 1966 to 1999 using the key words urinary tract infections, vesicoureteral reflux, child, and infant. As well, the recent practice parameter from the American Academy of Pediatrics (AAP) and the papers from the International Reflux Study in Children were carefully reviewed for both data and further references. Most of the data and recommendations provided are either from the large international multicentre studies in the International Reflux Study in Children or from the expert consensus opinions generated by the AAP. The remainder come from smaller studies, both prospective and retrospective.

### Diagnosis of and therapy for UTIs

Frequency, dysuria, urgency, and even hematuria are all difficult to assess in children, especially those younger than 2 or 3 years. Fever (>38°C orally) is common among children with UTIs, but is not universal. Children at greatest risk of serious illness secondary to UTIs (younger than 4 months) often fail to mount a fever even with a severe infection. Use of a urine dipstick can be helpful but is not diagnostic. Specifically, positive results for combined nitrite and leukocyte esterase tests give a sensitivity of 78% to .................................

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<table>
<thead>
<tr>
<th>Table 1. Take-home messages</th>
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<tbody>
<tr>
<td><strong>Rule 1</strong></td>
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<td><strong>Rule 2</strong></td>
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<td><strong>Rule 3</strong></td>
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<td><strong>Rule 9</strong></td>
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<tr>
<td><strong>Rule 10</strong></td>
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</tbody>
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Children’s UTIs in the new millennium

Table 2. Positive urine culture values

<table>
<thead>
<tr>
<th>CULTURE METHOD</th>
<th>POSITIVE CULTURE WHEN ONE ORGANISM GROWS (CFU/ML)</th>
<th>PROBABILITY OF TRUE INFECTION (%)</th>
<th>COMMENTS</th>
<th>CFU—colony-forming units. Data from Hellerstein.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprapubic aspiration</td>
<td>&gt; 1 x 10³</td>
<td>&gt;99</td>
<td>Any Gram-negative growth is positive</td>
<td></td>
</tr>
<tr>
<td>Catheterization</td>
<td>&gt; 1 x 10⁵</td>
<td>&gt;95</td>
<td>Infection unlikely if CFU/mL is below 10⁵; repeat culture and sensitivity tests</td>
<td></td>
</tr>
<tr>
<td>Clean catch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Boys</td>
<td>&gt; 1 x 10⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Girls</td>
<td>No. of specimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 1 x 10⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>80</td>
<td></td>
<td></td>
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</table>

92% and specificity of 60% to 98%, but the absence of either severely restricts the positive predictive value. Approximately 50% of children with culture-proven UTIs have negative nitrite results because young children in diapers void frequently. Positive results of esterase tests alone are neither sensitive nor specific enough to make a diagnosis. Therefore a urine culture is vital for diagnosing true UTI (rule 1 in Table 1).

Proper urine samples for culture, in non–toilet-trained children, are best obtained by catheter or suprapubic aspiration. Although bag specimens have excellent sensitivity (near 100%), if the prevalence of UTI is around 5%, the false-positive rate is anywhere from 85% to 99%. The negative predictive value is very high, however, so a sick child without toxemia but with a negative bag specimen is unlikely to have UTI. If the child is ill and has a positive bag culture or dipstick, or if you are planning to start antibiotics, then a proper urine sample should be obtained (ie, catheter or suprapubic aspiration) before therapy is started (rules 2, 3, and 4). Table 2 defines positive cultures, based on method used to obtain the sample.

The first step in treating children with UTIs is to determine whether they are ill or well, that is, to tolerate oral (vs parenteral) therapy. We treat young children (younger than 2 years) with broad-spectrum intravenous antibiotics (eg, ampicillin and either gentamicin or cefuroxime), especially if they are ill or unable to tolerate oral medications; we switch to oral therapy when the children improve. Obviously, initial antibiotic choices should be reevaluated in light of organism sensitivities and if children do not improve with treatment within 72 hours. At any age, children with toxemia, high fever, vomiting, or dehydration should be admitted to hospital for initial management.

Opinion and approach, however, are changing. In a recent randomized trial involving four American children’s hospitals, Hoberman and colleagues showed that an oral third-generation cephalosporin, used for outpatients aged 1 to 24 months with UTIs, provided the same outcomes and adverse events as 3 days of inpatient intravenous therapy. They then suggest that, for these patients, oral therapy can be cheaper than, and remain as safe and efficacious as, standard inpatient therapy. Fisher, however, points out that no truly ill children (with either hypotension or true toxemia) were enrolled in the study; their treatment with oral agents might have been contraindicated. On a cautionary note, 80% of patients were enrolled at the primary authors’ site.

At this time, standard care in most institutions promotes hospital admission for any child who appears to have toxemia, is younger than 2 years, or is unlikely to tolerate oral therapy. These patients should be treated with parenteral antibiotics until afebrile and well for at least 24 hours, then should complete their course with oral therapy (rule 5). This approach is supported in the current AAP guideline and by other authors.

Many studies of adults show that short antibiotic courses are effective for treating UTIs; these
supportive data do not apply to children. There is good evidence that 10 days of therapy is more beneficial than 3 days, but there is little evidence comparing the efficacy of 10 versus 14 days of intravenous and oral therapy (rule 6). Many pediatricians choose the 14-day course, especially for children who have toxemia. (The 14-day course is always chosen for children younger than 12 months who have toxemia because differentiation between simple cystitis and pyelonephritis is so difficult.)

When and how to investigate children with UTIs. This area is controversial. At the recent AAP consensus conference, the strength of evidence for radiologic investigations was only “fair.” The following are our own group’s interpretation of the data available; our recommendations mirror the recommendations of the AAP and the standard of care in most pediatric nephrology centres in Canada.

We divide children with proven UTIs into two groups, those older than 5 years and those younger than 5. We investigate older children with renal ultrasound to rule out structural anomalies and voiding cystourethrography. Children younger than 5 years (Figure 1) have renal ultrasound and voiding studies after their first UTI, including girls! Urinary tract infections in younger children can indicate an underlying genitourinary tract abnormality. In approximately 10% of these children, ultrasound shows abnormalities including hydronephrosis, renal scars, and ureteroceles.

For younger children, a voiding study is indicated for several reasons. Children presenting with UTIs...
than the general population: 30% compared with 1%. Vesicoureteral reflux in itself can predispose patients to develop renal damage and scarring. Both Jodal and Skoog and associates have shown increased risk of scar formation as grade of reflux increases, from as low as 5% with grade I to more than 50% with grade V reflux. Increasing grades of reflux carry increased risk of pyelonephritis. Finally, children younger than 5 years are at increased risk of damage from VUR (see below) and often have unrecognized infections. Therefore both investigations can show risk of developing, and presence of, renal scarring and damage (rule 7).

Whether to use a formal voiding cystogram or a radionuclide cystogram for follow up of reflux is controversial. For the initial study, however, a voiding cystogram has some advantages. It provides the grade of reflux as outlined by the International Reflux Study in Children, which is important both for prognoses and for predicting the likelihood of resolution. In male patients, it allows close examination of the urethra, which is needed to rule out posterior urethral valves, a potential cause of both VUR and serious renal damage. A voiding cystogram also delineates bladder anatomy and capacity, often important in neurogenic bladders. The radionuclide cystogram delivers slightly less radiation, but still requires catheterization. It tells whether reflux is still present or has resolved (rule 7). (Our few follow-up studies are usually done at parental request, as repeated testing does not change uncomplicated reflux management.) Other studies, such as radionuclide scans or furosemide renograms, should be offered only after subspecialty consultation with a pediatric nephrologist or urologist.

What to do for patients with vesicoureteral reflux? Because VUR increases the risk of both pyelonephritis and scarring, most current recommendations advocate prophylaxis against UTIs. This suggestion is based on the fact that pyelonephritic scarring is one of the most common causes of end-stage renal disease in many countries. In the United States, even with incomplete diagnostic coding for pyelonephritis, it remains among the top five causes of end-stage renal disease. No good controlled trials have looked at renal outcomes among children younger than 5 years with severe reflux comparing early treatment of UTIs with prevention through prophylaxis. In part this absence relates to concerns about possible long-term damage and to perceived low risk of prophylactic therapy. As Smellie mentions in a recent commentary, these attitudes could be changing, and soon true randomized trials could compare prophylaxis with treating these children’s infections. Until such trials appear, we recommend children younger than 5 years with reflux be started on antibiotic prophylaxis (rule 9).

Low-dose daily antibiotics reduce bladder colonization, and hence decrease the likelihood of sufficient bacterial growth to cause infection. Antibiotics must appear in the bladder, be effective against common urinary pathogens (Table 3), and be taken consistently (missed doses are the most common cause of therapeutic failure). Effectiveness of prophylaxis has varied from study to study, anywhere from 5% to 43% over 4 to 5 years of follow-up assessment. Levels of follow-up care seemed inversely related to the risk of recurrence quoted. Bacterial resistance remains a concern, most often due to penicillin or cephalosporin, followed by trimethoprim and then the least problematic drug, nitrofurantoin. In clinical practice, resistance does not substantially change the antibiotics available for therapy for most organisms and patients, nor does it increase the severity of breakthrough infections.

Antibiotic prophylaxis has been shown to be as effective as surgery in reducing scarring. Therefore surgery is contemplated only when antibiotics fail to prevent recurrent or severe UTIs or pyelonephritis, or when progressive damage or scarring can be documented. Children can discontinue antibiotics when reflux no longer occurs. Unfortunately, establishing the end of reflux requires a repeat voiding study, which is often

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE (MG/KG DAILY)</th>
<th>LIQUID PREPARATION (MG/ML)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrodantin* (nitrofurantoin)</td>
<td>1 given as one dose but not to children younger than 2-3 months</td>
<td>5</td>
</tr>
<tr>
<td>Septra* (trimethoprim-sulphamethoxazole)</td>
<td>0.5-1 of trimethoprim, given as one dose and not to children younger than 2-3 months</td>
<td>8 of trimethoprim component</td>
</tr>
<tr>
<td>Amoxil (amoxicillin)</td>
<td>5 given as one dose</td>
<td>25 or 50</td>
</tr>
<tr>
<td>Kellex (cephalexin)</td>
<td>12-15 given as one dose</td>
<td>25 or 50</td>
</tr>
</tbody>
</table>

*Preferred choices: nitrofurantoin is associated with less resistance but more gastrointestinal complaints than trimethoprim-sulphamethoxazole.
Editor's key points

- When you suspect a child has a urinary tract infection (UTI), obtain a proper culture specimen either by urinary catheterization or suprapubic aspiration if the child cannot provide midstream urine.
- There is fair evidence in favour of investigating by renal ultrasound and voiding cystogram all children younger than 5 years after their first UTIs.
- All children with reflux who are younger than 5 years should be treated with antibiotics for prophylaxis.

Points de repère

- Quand vous suspectez une infection urinaire basse chez un jeune enfant, une culture doit être obtenue par cathétérisme urinaire ou par ponction sus-pubienne si l’enfant n’est pas capable de fournir un mi-jet urinaire.
- Il existe des preuves d’assez bonne qualité en faveur d’une investigation à l’aide d’une échographie rénale et d’une cystographie mictionnelle chez tous les enfants de moins de 5 ans après leur première infection urinaire.
- Tous les enfants de moins de 5 ans présentant du reflux devraient recevoir une antibiothérapie prophylactique.

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References


unpleasant for children and is rarely performed any longer. We also stop antibiotics when children are no longer at high risk of damage from reflux. Children younger than 3 years (especially younger than 2) are at greater risk of damage from reflux of infected urine than those older than 3 years because of increased incidence of intrarenal reflux in younger children. Also the likelihood that infections go unnoticed likely contributes to increased risk of developing pyelonephritis, poor renal growth, and possibly renal scarring (rule 10).

Conclusion

Implicit within our discussion is the idea that we investigate and treat all young children with UTIs and VUR to reduce and prevent scarring and damage. A better process would be to identify children truly at risk of developing these complications, either at the beginning of therapy or before the problem arises. This goal would be both cost-effective and clinically more satisfying. Advances, such as prenatal diagnosis of serious renal anomalies; better diagnostic tests for UTIs in children; and inexpensive, noninvasive testing for reflux, will be important developments in this field.

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