POSITION STATEMENT

Prophylactic antibiotics for children with recurrent urinary tract infections

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Abstract

Prophylactic antibiotics for urinary tract infections are no longer routinely recommended. A large number of children must be given prophylaxis to prevent one infection and antibiotic resistance is a major concern when treating community-acquired urinary tract infections. The results of three recent significant studies are examined, with focus on the efficacy of prophylaxis, and recommendations are made.

Key Words: Antibiotic resistance; Antibiotic stewardship; Renal scarring; UTI; VUR

Urinary tract infections (UTIs) are a common cause of acute illness in infants and young children, occurring in an estimated 8% of girls and 2% of boys by seven years of age, with a recurrence rate of 10% to 30%.[1] Guidelines and recommendations for diagnosing UTIs were recently updated by the Canadian Paediatric Society and should be consulted for how to sample and test urine, how to interpret results and for treatment strategies.[2] The present position statement examines published data regarding the efficacy of prophylaxis following a UTI in infants and young children.

Is prophylaxis ever indicated?

The premise of antibiotic prophylaxis for UTIs is that it can prevent UTIs and long-term sequelae (eg, hypertension and renal failure).[3] Traditional thinking is that infants and young children who are diagnosed with vesicoureteral reflux (VUR) of any grade are at increased risk for recurrent UTIs and, therefore, require antibiotic prophylaxis.[4] However, many older studies investigating antibiotic prophylaxis were small and of poor quality.[5] Also, because a stringent definition of UTI was not used, they tended to overestimate the efficacy of prophylaxis.[6] Even if prophylaxis is effective, there is increasing doubt that recurrent UTIs in children with normal kidneys lead to long-term sequelae, even when such infections result in renal scarring.[7]

The American Academy of Pediatrics Subcommittee on Urinary Tract Infection published updated clinical practice guidelines in 2011. Their meta-analysis of six studies that included children <24 months of age did not show a significant benefit of antibiotic prophylaxis, either in infants without VUR or in those with grades I to IV VUR. The sample size was small for some subgroups in these studies.[6] However, a Cochrane meta-analysis of 12 studies that included children in varying age groups indicated that if the largest and best-designed studies (Montini et al,[8] published in 2008, and the Prevention of Recurrent urinary tract Infection in children with Vesicoureteric Reflux and Normal Renal Tracts [PRIVENT] trial,[9] published in 2009) were combined, there was a small but significant decrease in recurrent UTIs in the prophylaxis group, independent of VUR.[10]

Recently, the results of the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial were published.[11] Table 1 summarizes the details of this trial along with results from the two previously completed large trials (Montini et al[8] and the PRIVENT trial[9]) including a total of 1521 enrolled children with ≥1 previous UTIs. The RIVUR trial[11] enrolled only children with VUR and followed them for two years, while the other two trials enrolled children with or without VUR (including some children who were never assessed for VUR) and followed them for one year. Montini et al[8] excluded children with proven grades IV or V VUR. The PRIVENT trial enrolled children of all ages, while the age limit for the other two trials was seven years (Montini et al) and 71 months (RIVUR). There was a striking predominance of girls in the RIVUR trial (92%). Montini et al used bagged urines for children who were not toilet trained and required two samples suggestive of a UTI, while the two other trials re-

quired a single catheter or suprapubic specimen for such children. The definitions of UTI in the three studies also varied. Only Montini et al required fever, and only the PRIVENT trial did not require pyuria. The Montini et al trial was not blinded and did not include a placebo, while the other two did both. The primary outcome in all three trials was a single recurrent UTI.

Given the heterogeneity in study design, it is not surprising that the results of the trials differ (Table 1). The efficacy of antibiotic prophylaxis was very low in the Montini et al trial.[8] The other two trials demonstrated higher efficacy, but if it is assumed that patients lost to follow-up did not have UTIs, antibiotics would have to be prescribed for one year for 17 children with UTI with or without VUR (PRIVENT[9]) or for two years for nine children with VUR (RIVUR[11]) to prevent recurrent UTIs in one child. As expected, the Montini et al and RIVUR trials described a much higher rate of recurrences among children with grade III or higher VUR than in other children. The relationship between VUR and recurrences was not reported in the PRIVENT trial. The sample size of the studies was too small to demonstrate whether the efficacy of prophylaxis is the same with all grades of reflux. All three trials found a similar low rate of worsening of renal scarring in both cases and controls. The median time to recurrence in both groups in the Montini trial was 113 days. One-half of the recurrences in the placebo group in the PRIVENT study occurred within three months and three-quarters occurred within six months.

Minor adverse drug reactions were reported in 7% of children on prophylaxis in the Montini et al[8] trial. It was not clear whether medication was then stopped. Medication was stopped in 1.4% of cases and 3.5% of controls in the PRIVENT trial[9], and in 2.3% of cases and 2.0% of controls in the RIVUR trial[11] for suspected adverse drug reactions, suggesting that trimethoprim-sulfamethoxazole was well tolerated. Few children were lost to follow-up (approximately 8% in Montini et al, 2% in PRIVENT and 6% in RIVUR). However, noncompliance was suspected in approximately 25% of cases in all three trials. This occurred almost equally in cases and controls in the PRIVENT and RIVUR studies, and suggests that compliance with long-term antibiotic prophylaxis outside of a study setting is likely to be suboptimal, further limiting efficacy.

None of the studies referenced in the present statement were powered to compare the efficacy or safety of different prophylactic antibiotics. Some studies suggest that treating with nitrofurantoin may prevent more UTIs than trimethoprim-sulfamethoxazole, but this drug is associated with gastrointestinal side effects.[10] Developing local resistance to the antibiotic prescribed was a common finding in studies in which this was assessed.[8][10][11]

Summary

The vast majority of children receiving UTI prophylaxis do not benefit. There is no evidence that prophylaxis prevents renal scarring or other long-term sequelae. Moreover, there is increasing evidence that recurrent UTIs do not contribute to chronic renal failure in children with no structural renal anomaly.[7] Therefore, more harm than benefit may result from prophylaxis. Long-term antibiotics may cause adverse events as well as promote resistance to all available oral antibiotics. Managing constipation appropriately may be helpful for decreasing UTI recurrences.[12] It is important for clinicians to inform the parents of a child who has had a UTI about the risk and signs or symptoms of a recurrence, and urge them to seek prompt diagnosis and therapy when suspicions arise.

Recommendations

- Antibiotic prophylaxis is no longer routinely recommended after a UTI but may still be considered when a child is known to have a grade IV or V VUR, or a significant urological anomaly. A large number of children must be treated to prevent one UTI, although this number may be smaller for children with grade IV or V VUR, or a significant urological anomaly. An increasing risk for antibiotic resistance may soon negate the benefits of prophylaxis even in these cases.
- For cases in which prophylaxis is still used, it should generally last for no longer than three to six months. If the abnormality persists, prophylaxis should be reassessed. Antibiotic resistance increases with prolonged prophylaxis.
- If the decision is made to offer prophylaxis to children with grade IV or V VUR, or a major urological anomaly, the risks and benefits should be discussed with parents.
- Trimethoprim/sulfamethoxazole or nitrofurantoin are the usual choices for prophylaxis, unless contraindicated or the child has already had urinary isolates test positive for resistance to these drugs. These antibiotics are inexpensive, generally well tolerated and disrupt bowel flora less than most others. Nitrofurantoin is no longer commercially available as a suspension and parents will need to be referred to a compounding pharmacy to obtain it. They can also be advised to crush the pills and mix the powder with yogurt or apple sauce. There is insufficient evidence to recommend a specific dose; however, traditionally, one-

quarter to one-third of the daily total treatment dose is given once per day. There are no data on the efficacy of the practice of alternating prophylactic antibiotics on a monthly basis.

- Prophylaxis should be stopped or changed if an organism that is resistant to the prophylactic antibiotic is identified in a urine culture, even when the culture is believed to be contaminated. That antibiotic is highly likely to be ineffective in preventing UTIs and continuing to use it will promote development of further resistance. If a child has a urinary isolate that is resistant to both trimethoprim/sulfamethoxazole and nitrofurantoin, consider discontinuing prophylaxis. Experience suggests that using broader-spectrum agents for prophylaxis (such as cefixime or ciprofloxacin) often results in a UTI with an organism that is resistant to any remaining oral options for therapy.
- Cases with grade IV or V VUR, or another significant urological anomaly, should be discussed with or seen by a paediatric nephrologist or urologist.
- Parents of a child who has had a UTI need to be informed of the signs and symptoms of a recurrence. The threshold should be low for testing for a UTI in such children.

Table 1

Incidence of recurrent urinary tract infections (UTIs) in the three largest published trials of antibiotic prophylaxis

Study	Age of children enrolled	Inclusion criteria	UTI definition	Intervention	Sample size	Patients with UTIs			Relative risk of UTI in group on prophylaxis		NNTP
						All patients*	Prophylaxis group*	Control group*			
Montini et al [8], 2008; Italy	2 months to 7 years	One febrile UTI; excluded if the child had a complex urological malformation or severe renal damage	Fever AND either elevated ESR/CRP or elevated neutrophil count AND 2 urines with: pyuria AND $\geq 10^8$/L of a single organism	TMP-SMX or amoxicillin-clavulanate†	211 cases; 127 controls	27/312 (8.7%) Subgroups: No VUR: 8/210 (3.8%) Grade I or II VUR: 7/88 (4.3%) Grade III VUR: 12/40 (30%)		15/211 (7.1%) Subgroups: No VUR: 5/129 (3.9%) Grade I or II VUR: 4/56 (7.1%) Grade III VUR: 6/26 (23.1%)	12/127 (9.5%) Subgroups: No VUR: 3/81 (3.7%) Grade I or II VUR: 3/32 (9.4%) Grade III VUR: 6/14 (42.9%)	0.75 (95% CI 0.36–1.55; P=0.44)	42
PRIVENT [9], 2009; Australia	Birth to 18 years	One or more symptomatic UTIs at any time in the past; excluded if the child had a urological predisposing cause	UTI symptoms (not defined) AND positive urine culture‡	TMP-SMX (controls received TMP-SMX for only the first 14 days)	288 cases; 288 controls	91/576 (16%)		36/288 (13%) Subgroup: febrile recurrences 19/288 (7%)	55/288 (19%) Subgroup: febrile recurrences 36/288 (13%)	0.65 (95% CI 0.44–0.96; P=0.03)	17
RIVUR [11], 2014; United States	2 to 71 months	One or two UTIs within the last 112 days with grade I – IV VUR and no urological anomalies	Pyuria, positive urine culture§, AND fever or urinary symptoms¶	TMP-SMX	302 cases; 305 controls	111/607 (18.2%) Grade I or II VUR: 46/322 (14.3%) Grade III or IV VUR: 64/280 (22.9%)		39/302 (12.9%)	72/305 (23.6%)	0.55 (95% CI 0.38–0.78)	9

CRP C-reactive protein; ESR Erythrocyte sedimentation rate; NNTP Number of children needed to treat to prevent one UTI during study follow-up (one year in the Montini et al[8] and PRIVENT[9] studies and two years in the RIVUR[11] study; TMP-SMX Trimethoprim-sulfamethoxazole (also known as cotrimoxazole); VUR Vesicoureteral reflux. *Results assume that patients lost to follow-up did not experience recurrences because this is the only analysis reported in the PRIVENT study; †The original plan was to compare the two antibiotics; however, recruitment was slow and this plan was abandoned. Both antibiotics were dosed at 15 mg/kg/day, presumably of the TMP component for the TMP-SMX; ‡Any growth from a suprapubic aspiration urine specimen, $\geq 10^7$/L of a single organism from a catheter sample or $\geq 10^8$/L of a single organism for clean voided specimens; §Single organism that was neither Lactobacillus nor Candida, at $\geq 5 \times 10^7$/L for catheterized or suprapubic aspiration urine specimens or $\geq 10^8$/L for clean voided specimens; ¶Suprapubic, abdominal or ank pain or tenderness; urinary urgency, frequency or hesitancy; dysuria; foul-smelling urine; or, in infants younger than 4 months of age, failure to thrive, dehydration or hypothermia

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