

Are prophylactic antibiotics indicated after a urinary tract infection?

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Purpose of review

Many children with urinary tract infection (UTI) and urinary tract abnormality such as vesicoureteral reflux (VUR) are given prophylactic antibiotic to prevent recurrence of UTI and permanent kidney damage. Occasionally, children with normal urinary tract receive prophylactic antibiotic to alleviate the patient suffering and family inconvenience associated with recurrent symptomatic UTI. These recommendations are mostly opinion-based and are derived from studies that were not randomized and were done before the current renal imaging modalities became available. The purpose of this review is to discuss these recommendations in the context of recent research findings.

Recent findings

Recent studies have raised serious doubts about the role of antibiotic prophylaxis after UTI by demonstrating the presence of preexisting renal scars without UTI in some patients, systematic reviews of published literature on UTI and VUR, and by comparing randomized patients with VUR who received antibiotic prophylaxis with those who did not receive any prophylaxis. However, the new knowledge has also highlighted that, apart from skilful management of individual patients, well designed studies are needed to answer the questions on antibiotic prophylaxis across the spectrum of UTI in different clinical situations. One such study currently underway is the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study, which will evaluate the role of antibiotic prophylaxis in preventing recurrent UTI and renal scarring in young children with VUR.

Summary

It is advisable that, until the results of more appropriately designed studies become available, UTI in young children is considered as a risk factor for renal scarring and each patient is treated with prudence.

Keywords

prophylactic antibiotic, urinary tract infection, vesicoureteral reflux

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Introduction

The use of prophylactic antibiotic after urinary tract infection (UTI) in a pediatric patient depends on multiple factors such as patient age, first-time versus recurrent UTI, coexisting urological abnormality such as vesicoureteral reflux (VUR) or neurogenic bladder or the presence of voiding dysfunction. Many children with asymptomatic bacteriuria are wrongly prescribed repeated courses of therapeutic antibiotic for suspected UTI and even receive antimicrobial prophylaxis. It is beyond the scope of this review to discuss antibiotic prophylaxis following UTI in all possible clinical situations. This review will focus on the current knowledge regarding antibiotic prophylaxis in preventing recurrent UTI, renal damage, or both in young children with UTI with and without VUR.

Up to 7% of girls and 2% of boys have culture-proven and symptomatic UTI by 6 years of age [1]. UTI recurs in about 75% of children with first UTI in infancy and in about 40% of girls and 30% of boys with first UTI after the age of 1 year [2^{*}]. Prophylactic antibiotics are used mostly in children with urological anomalies, such as VUR, to prevent recurrence of UTI and renal parenchymal damage, which carries a risk of subsequent hypertension, toxemia of pregnancy, and end-stage renal disease. In some children with normal renal anatomy and a very low risk of renal parenchymal damage, prophylactic antibiotics are prescribed to decrease the frequency of recurrent symptomatic UTI that distress the patient and are disruptive to the family life. Numerous studies in the past have weighed heavily in support of antibiotic prophylaxis after UTI. However, recent research has raised significant doubts about such practice.

Urinary tract infection without vesicoureteral reflux

In a systematic review of six randomized trials on antimicrobial prophylaxis after UTI, which included three trials on children with anatomically normal urinary tracts, the rate of infections for children with normal urinary tracts ranged from zero to four per 10 patient-years for the treatment groups and from 4.0 to 16.7 for the control groups. The study [3] concluded that the available evidence for using antimicrobial prophylaxis to prevent UTI in children with normal urinary tract is of low quality, and it emphasized a need for well designed trials to optimize the use of antimicrobials in children with recurrent UTI. Similar conclusions were made by Cochrane 2006 review [4], which identified eight studies, five (406 patients) of which compared antibiotic with placebo/no treatment. The duration of antibiotic prophylaxis ranged from 10 weeks to 12 months. Even though the review revealed that, compared with placebo/no treatment, antibiotics reduced the risk of repeat positive urine culture, the evidence to support the widespread use of antibiotics to prevent recurrent symptomatic UTI was found to be very weak [4]. In an opinion-based simplistic recommendation for healthcare professionals in the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) recommended that 'antibiotic prophylaxis should not be routinely recommended in infants and children following first-time UTI' [2*].

A recent retrospective analysis [5*] of medical records of a large cohort of 74 974 children 6 years of age or younger reported some interesting observations. These children were seen in the primary care setting over a period of 5 years. Of the children included in the study, 666 had first UTI and of these 83 had recurrent UTI (20/83 patients had no VUR). The significant predictors for recurrence of UTI in this population included white race, age 3–5 years, and grades 4–5 VUR; child sex, lower-grade VUR, and antimicrobial exposure were not risk factors. Use of antimicrobial prophylaxis caused no significant delay between the initial UTI and first recurrence. It revealed that there was a 7.5-fold increased likelihood of a resistant pathogen causing the recurrence. The study [5*] concluded that, among the children in this study, antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.

Urinary tract infection with vesicoureteral reflux

The natural history of the VUR is to improve or resolve completely with time in most of the patients. The traditional management consists of prompt treatment of UTI, long-term antimicrobial prophylaxis until the resolution of VUR, or surgical intervention in those with

persistent high-grade VUR, recurrent UTI in spite of prophylactic antimicrobial agent, allergy to antimicrobial agent, and child/parent noncompliance with the medical management.

The use of antimicrobial prophylaxis in the prevention of renal injury in young children with VUR has been endorsed by many professional societies such as the American Academy of Pediatrics (AAP) [6], the Swedish Medical Research Council [7], and the American Urological Association (AUA) [8]. These recommendations are based on the severity of VUR, unilateral versus bilateral VUR, presence or absence of renal scarring on initial evaluation or during follow-up, and the clinical course of VUR. Some of the recommendations are contradictory. Although AUA [8] recommended prophylactic antibiotic for low-grade VUR, the Swedish Medical Research Council [7] advocated no antibiotic prophylaxis in such patients. However, both emphasized the importance of renal scarring in decision-making. The AAP [6] guidelines recommend continuation of antimicrobial prophylaxis after treatment of acute UTI until imaging studies are reviewed and a decision made about further management.

Controversies over antimicrobial prophylaxis in vesicoureteral reflux

Shindo *et al.* [9] reported progression of renal scarring despite correction of the VUR and prevention of UTI. Arant [10] reported that, in spite of good medical management, even mild and moderate VUR can be associated with renal injury. Cooper *et al.* [11] reported no new renal scars when antibiotic prophylaxis was discontinued in children with grades I–IV VUR. Other reports that have raised doubts about the role of long-term antimicrobial prophylaxis include the observation that up to half of patients with severe VUR exhibit no evidence of renal damage [12], incidence of renal scars does not always match the severity of VUR [13], and the frequency of pyelonephritis is similar with and without the resolution of VUR [14].

In a systematic analysis that compared antibiotics with placebo or no treatment for preventing UTI in susceptible children, Williams *et al.* [15] concluded that most published studies to date have been poorly designed with biases known to overestimate the true treatment effect. Another systematic analysis [16], which evaluated the value of identification of VUR after a symptomatic UTI and the effects of various interventions on the occurrence of UTI and subsequent renal parenchymal damage, concluded that it is uncertain whether the identification and treatment of children with VUR confers clinically important benefit and any intervention, including antibiotic prophylaxis or surgery for VUR, is better than no treatment. Yet another systematic analysis [17], which

evaluated the predictability of renal parenchymal damage by diagnosing VUR in hospitalized children with febrile UTI, revealed VUR to be a weak predictor of renal damage in such children.

Antibiotic prophylaxis versus surveillance only

Recently, a few studies have compared antibiotic prophylaxis with surveillance only in children with primary VUR. Garin *et al.* [18] studied 236 children aged 3 months to 18 years with acute pyelonephritis. Of these, 218 completed 1-year follow-up. One hundred and thirteen children (age group 3 months to 12 years) with grades I–III VUR and 105 children without VUR (age group 3 months to 17 years) were included in the study. Patients were randomly assigned to prophylactic antibiotic or no prophylaxis. Dimercaptosuccinic acid (DMSA) renal scans were done to document renal scarring. At the end of 1 year, only 13 (5.9%) of the 218 children had developed renal scarring, and no difference was noted in the incidence of UTI, pyelonephritis, or renal scarring between the prophylaxis and no-prophylaxis groups [18]. In another study, Roussey-Kesler *et al.* [19^{*}] randomized 225 children with grades I–III VUR to daily antibiotic prophylaxis or no prophylaxis. The age of the children ranged from 1 month to 3 years. After a follow-up period of 18 months, there was no significant difference in the occurrence of UTI (17% in treatment group and 26% in untreated control group; $P=0.2$) between the two groups. No difference on the basis of the grade of VUR was noted. A significant association was found between treatment and child sex ($P=0.017$), with significantly reduced UTI in boys on prophylaxis, particularly in those with grade III VUR [19^{*}]. In a third randomized study, Pennesi *et al.* [20^{*}] recruited 100 children with grades II–IV VUR diagnosed after a first episode of acute pyelonephritis. Children were randomly assigned to receive antibiotic prophylaxis or no prophylaxis. The mean ages of children in the prophylaxis and no-prophylaxis groups were 9 and 8.3 months, respectively. At the end of 2 years, prophylaxis was discontinued and patients were followed for another 2-year period, for a total follow-up period of 4 years. DMSA renal scans were done to diagnose renal scars. There was no difference in recurrence of acute pyelonephritis at the 2-year (36 versus 30% for prophylaxis and no prophylaxis, respectively) or 4-year period. DMSA renal scans were abnormal in 0, 30, and 67% of children with grade II, III, and IV VUR, respectively. No significant difference in renal scarring was noted at 2 years and no patients were noted to have new renal scars during the 4-year period [20^{*}]. These important studies on the one hand did not support any role for prophylactic antibiotic in the prevention of recurrent UTI, the development of renal scars, or both after acute pyelonephritis in some children with or without VUR, but on the other hand they did not invalidate the role of prophylaxis in all children with VUR. Further-

more, the studies had limitations that included lack of blindness, number of children studied, urine collection methods in nontilet-trained children, relatively short duration of follow-up, and wide age group in one study. Also, none of the studies addressed in depth the issue of interobserver variability in the interpretation of DMSA renal scans.

Limitations of antimicrobial prophylaxis

The long-term antimicrobial prophylaxis has its limitations. It is not always effective; the breakthrough UTI rates in children with VUR range from 25 to 38% [14,21]. Antimicrobial resistance is a major concern with long-term antimicrobial prophylaxis. In one study [22], children who received the medication for more than 4 weeks in the preceding 6 months had more resistant *Escherichia coli* when compared with those not on such treatment [odds ratio (OR) 13.9, 95% confidence interval (CI) 8.2–23.5]. In another study [22] on childhood UTI, a generalized decrease in bacterial susceptibility to common antibiotics was seen in the year 1999 when compared with those previously seen in 1991. Approximately 10% of children on long-term prophylaxis have adverse reactions, most of which occur within the first 6 months. These include gastrointestinal symptoms, skin rashes, hepatotoxicity, and hematological complications with sulfamethoxazole/trimethoprim (SMZ-TMP) and mostly gastrointestinal symptoms with nitrofurantoin. More adverse reactions such as marrow suppression, and rarely Stevens–Johnson syndrome, may also occur with SMZ-TMP [23,24]. Compliance with daily administration of the medication over a prolonged period of time is questionable. In one study [25], 97% of the parents reported compliance with low-dose daily antimicrobial prophylaxis and yet the medicine was found in only 31% of the children's urine. Other concerns with long-term antimicrobial prophylaxis are the children's inconvenience, with repeated follow-up voiding cystourethrogram (VCUG) examinations to monitor the VUR resolution, and the cost of the procedure.

Conclusion

The use of prophylactic antibiotic following UTI, particularly in young children with VUR, has been a common practice for decades. This recommendation, which is mostly opinion-based, was derived from studies that were not randomized and were done before the current renal imaging modalities became available. Recent knowledge about the presence of preexisting renal scars without UTI in some patients and the role of constipation and voiding dysfunction in UTI, as well as the recent clinical trials and systematic reviews, has raised serious doubts about the role of antibiotic prophylaxis. However, new knowledge has also revealed that, apart

from skilful management of individual patients, more well designed studies are needed to help answer the questions on antibiotic prophylaxis across the spectrum of UTI in different clinical situations. One such study currently underway is the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study, which is a multicenter, prospective, randomized, placebo-controlled study that will evaluate the role of prophylactic antibiotic in preventing recurrent UTI and renal scarring in young children with VUR. As prevention of renal scars following UTI remains the most important objective, it is advisable that, until the results of more appropriately designed studies become available, VUR and UTI be considered as risk factors for renal scarring and each child be treated with prudence.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 277).

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