Consensus and Controversies in Antibiotic Prophylaxis for Urinary Tract Infections

Rehna K Rahman¹, Nivedita Kamath²

ABSTRACT

Antibiotic prophylaxis in children with urinary tract infection is controversial. There is some evidence to show that antibiotic prophylaxis reduces the risk of infection in children with vesicoureteral reflux and recurrent UTI. However, there is also an increased risk of urinary tract infection by resistant organisms in children on long term antibiotic prophylaxis. Little is known about the benefit of antibiotic prophylaxis in reducing the risk of scars and long term sequelae of urinary tract infections.

Keywords: Antibiotic prophylaxis, Urinary tract infection, Vesicoureteric reflux.

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INTRODUCTION

Febrile urinary tract infection (UTI) is a common infection in children.¹ Unlike most other acute bacterial infections, febrile urinary tract infections are associated with renal scarring in about 19% of children.² Though the exact incidence of end stage renal disease attributable to recurrent UTI and renal scarring is not well known, a retrospective analysis of young adults showed that pyelonephritis in childhood was associated with a four times higher risk of end-stage renal disease (ESRD) in adulthood.³ Given the potential serious long-term outcome of childhood urinary tract infection, prevention of UTI in children who are at risk becomes a priority.

Long-term, low dose continuous antibiotic prophylaxis (CAP) is one of the many ways to prevent UTI. It has been recommended on the premise that it can prevent recurrent UTI and therefore prevent renal scarring and its sequelae. However, there is more controversy than consensus on the use of antibiotic prophylaxis in the prevention of recurrent UTI and its sequelae. In this review, we discuss the common indications for antibiotic prophylaxis, the recommendations and the controversies surrounding the use of antibiotic prophylaxis for urinary tract infections in children.

INDICATIONS FOR ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis is recommended in children who are at risk for recurrent urinary tract infections and renal scarring. Recurrent UTI is defined as the second episode of UTI.⁴ About 78% of girls and 71% of boys who had the first episode of UTI are at risk for recurrent UTI.⁵

A systematic review showed that 5–15% of children had scarring in the first 1–2 years following the first UTI. New scars were seen in 2–23% and progression of existing scars in 6–34% of these children and recurrent UTI was a significant risk factor for new/progressive scars.⁶

The most common clinical indications for antibiotic prophylaxis are⁷

- Recurrent urinary tract infections with or without vesico-ureteric reflux
- Vesico-ureteric reflux with or without urinary tract infection
- Neonates and infants with the first episode of urinary tract infection
- Antenatal hydronephrosis

COMMONLY USED ANTIBIOTICS

Urinary tract infection is most often an ascending infection by organisms from the gastro-intestinal tract or from organisms colonizing the peri-urethral or preputial areas. Antibiotic prophylaxis is given with the aim of reducing bacterial proliferation in the bladder by providing an adequate inhibitory antibiotic level in the bladder.⁷ Antibiotics which achieve high urinary concentrations with low serum levels and low impact on the normal gut and peri-urethral flora are ideal choices for prophylaxis. Prophylaxis is usually administered as a single night time dose, to facilitate its concentration in the bladder and enhance efficacy. Prophylactic antibiotics are administered at a dose that is 25–30% of the original dose.⁸

The most commonly used antibiotics are cephalaxin, cotrimoxazole and nitrofurantoin. The doses of the commonly used antibiotics and their adverse effects are given in Table 1.⁴ Cotrimoxazole (trimethoprim-sulphamethoxazole) has been used effectively as a prophylactic agent for a longtime. Trimethoprim achieves high inhibitory concentration in the bladder without significant effect on the commensals. Most of the side effects of the drug are attributed to the sulphamethoxazole component. The most serious adverse effects are toxic skin reactions and bone marrow suppression.⁸ Nitrofurantoin achieves high bladder concentration and has little effect on colonic bacteria. The drug requires modification of dose in renal failure. The common side effects are gastro-intestinal-nausea, vomiting, etc. Nitrofurantoin should be avoided in children with reduced renal function.⁸

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First generation or second generation cephalosporins have been used for uroprophylaxis. They are safe, have minimal side effects and can be used in infants <3 months of age and those with reduced renal function.

A randomized controlled trial comparing cotrimoxazole and 2nd generation cephalosporins showed that both are equally efficacious in UTI prophylaxis but cephalosporins had increased risk of bacterial resistance.9

**Disadvantages of Antibiotic Prophylaxis**

The common adverse effects of the drugs used for prophylaxis are listed in Table 1.

The most serious disadvantage of antibiotic prophylaxis is the increase in antibiotic resistance and the risk of subsequent febrile UTI by resistant organisms. Antibiotic prophylaxis needs to be administered over a long period of time and this may result in poor compliance. Recurrence of UTI by an organism that is sensitive to the prophylactic agent is a sign of non-compliance.

**Duration of Antibiotic Prophylaxis**

The duration of antibiotic prophylaxis depends on the indication for which the prophylaxis was considered. There are no clear guidelines as to when to consider stopping prophylaxis. Generally, the risk of scarring following a UTI is reduced after the age of 5 years.7

**Antibiotic Prophylaxis in Specific Conditions**

The recommendations by various guidelines for antibiotic prophylaxis in the common clinical indications are given in Table 2.4,10–13

Most guidelines do not recommend routine antibiotic prophylaxis following the first episode of UTI. In children with recurrent UTI, the NICE guidelines recommend antibiotic prophylaxis if there is a significant risk of UTI despite self-care and other conservative measures and the need to continue prophylaxis must be re-assessed every 6 months. However, the ISPN guidelines are more liberal in their recommendation of antibiotic prophylaxis, perhaps considering the risk of poor follow-up in our population.

Similarly, for antenatal hydronephrosis, the Indian guidelines recommend the use of antibiotic prophylaxis until the etiology is ascertained or the hydronephrosis resolves.

In other urological conditions like obstructive uropathy, neurogenic bladder, children on clean intermittent catheterization and voiding dysfunction, there are no clear guidelines on the use of antibiotic prophylaxis. The risk of development of UTI by resistant organisms outweighs the benefit of uroprophylaxis. In children on clean intermittent catheterization, use of antibiotic prophylaxis increased the rate of infections and these infections were by resistant organisms.14

**Evidence for Antibiotic Prophylaxis**

The key clinical trials in recurrent UTI and VUR, systematic review on antibiotic prophylaxis in antenatal hydronephrosis and Cochrane review on long term antibiotic prophylaxis are summarized in Table 3.

Most of the clinical trials on VUR excluded the grade V VUR children who are at the highest risk for UTI and scarring. Hence, the results of these studies may not be applicable to these children. Though the recent trials showed a significant reduction in UTI, there

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**Table 1:** Commonly used drugs for antibiotic prophylaxis in children with UTI8

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/kg/day)</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalixin</td>
<td>10</td>
<td>Minimal</td>
</tr>
<tr>
<td>Cephadroxil</td>
<td>5</td>
<td>Minimal</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>1–2 (of trimethoprim)</td>
<td>Avoid in infants &lt;3 months, G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic skin reaction, bone marrow suppression—rare</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1–2</td>
<td>Avoid in infants &lt;3 months, G6PD deficiency, renal failure</td>
</tr>
</tbody>
</table>

**Table 2:** Guidelines on antibiotic prophylaxis in specific conditions4,10–13

<table>
<thead>
<tr>
<th>Indication for antibiotic prophylaxis</th>
<th>NICE guidelines</th>
<th>AAP guidelines</th>
<th>ISPN guidelines</th>
<th>Other guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of UTI in infancy</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Recommended</td>
<td></td>
</tr>
<tr>
<td>Recurrent UTI</td>
<td>May be considered</td>
<td>Not recommended unless the child is an infant or is with VUR</td>
<td>Recommended</td>
<td>AUA and EAU recommend in infants until they are toilet trained and BBD is ruled out</td>
</tr>
<tr>
<td>Vesico-ureteric reflux</td>
<td>Recommended in young children with higher grades of VUR (grades IV and V)</td>
<td>Recommended in grade I–II VUR till 1 year of age; to restart if breakthrough UTI occurs later</td>
<td>In grade III–V VUR till 5 years of age</td>
<td></td>
</tr>
<tr>
<td>Antenatal hydronephrosis</td>
<td></td>
<td></td>
<td></td>
<td>Recommended in postnatally confirmed moderate to severe HN (SFU 3–4, renal APD &gt; 10 mm) or ureteric dilatation awaiting evaluation</td>
</tr>
</tbody>
</table>

NICE, National Institute of Health and Care Excellence; AAP, American Academy of Pediatrics; ISPN, Indian Society of Pediatric Nephrology; AUA, American Urology Association; EAU, European Association of Urology; HN, hydronephrosis; BBD, bowel bladder dysfunction
was no significant reduction in the prevalence of renal scarring.\textsuperscript{15–17}

The recent Cochrane analysis on long-term antibiotic prophylaxis in recurrent UTI showed that there is a modest reduction in symptomatic UTI. But the data regarding antibiotic resistance was reported only in a few studies and the evidence was therefore inconclusive.\textsuperscript{18}

To summarize, there is moderate evidence to show that antibiotic prophylaxis is more effective than placebo in reducing the risk of recurrent UTI in children. Though there is some evidence of reduction of renal scars, the evidence is not conclusive. The risk of antibiotic resistance is higher in children on antibiotic prophylaxis, however, the evidence is inconclusive.\textsuperscript{19}

The systematic review on uroprophylaxis in antenatal hydronephrosis showed that the antibiotic prophylaxis may be useful in reducing the risk of UTI in children with higher grades of hydronephrosis, ureteral dilatation and in male children who are uncircumcised.\textsuperscript{20} But the lack of randomized controlled trials in children with antenatal hydronephrosis and the heterogeneity of the underlying etiology of antenatal hydronephrosis are confounding factors.\textsuperscript{21}

**CONCLUSION**

Based on the recent evidence, we can conclude that antibiotic prophylaxis has a role in reducing UTI in children with VUR and recurrent UTI. There is an increased risk of antibiotic resistance, but this is not seen consistently across various studies. The question as to whether antibiotic prophylaxis reduces the risk of renal scarring and subsequent risk of chronic kidney disease still remains unanswered.

**REFERENCES**


