

# Consensus and Controversies in Antibiotic Prophylaxis for Urinary Tract Infections

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## ABSTRACT

Antibiotic prophylaxis in children with urinary tract infection (UTI) is controversial. There is some evidence to show that antibiotic prophylaxis reduces the risk of infection in children with vesicoureteric reflux (VUR) and recurrent UTI. However, there is also an increased risk of UTI 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.<sup>1</sup> Unlike most other acute bacterial infections, febrile urinary tract infections are associated with renal scarring in about 19% of children.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> About 78% of girls and 71% of boys who had the first episode of UTI are at risk for recurrent UTI.<sup>5</sup>

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.<sup>6</sup>

The most common clinical indications for antibiotic prophylaxis are<sup>7</sup>

- Recurrent urinary tract infections with or without vesicoureteric reflux
- Vesicoureteric reflux with or without urinary tract infection
- Neonates and infants with the first episode of urinary tract infection
- Antenatal hydronephrosis

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## COMMONLY USED ANTIBIOTICS

Urinary tract infection is most often an ascending infection by organisms from the gastrointestinal tract or from organisms colonizing the periurethral 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.<sup>7</sup> Antibiotics which achieve high urinary concentrations with low serum levels and low impact on the normal gut and periurethral 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.<sup>7,8</sup>

The most commonly used antibiotics are cephalexin, cotrimoxazole and nitrofurantoin. The doses of the commonly used antibiotics and their adverse effects are given in Table 1.<sup>4</sup>

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 sulfamethoxazole component. The most serious adverse effects are toxic skin reactions and bone marrow suppression.<sup>8</sup>

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.<sup>8</sup>

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.<sup>9</sup>

**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 noncompliance.

**DURATION OF ANTIBIOTIC PROPHYLAXIS**

The duration of antibiotic prophylaxis depends on the indication for which the prophylaxis was considered. There are no clear guidelines

**Table 1:** Commonly used drugs for antibiotic prophylaxis in children with UTI<sup>4</sup>

Drugs	Dose (mg/kg/day)	Adverse effects
Cephalexin	10	Minimal
Cephadroxil	5	Minimal
Cotrimoxazole	1–2 (of trimethoprim)	Avoid in infants <3 months, G6PD deficiency Toxic skin reaction, bone marrow suppression—rare
Nitrofurantoin	1–2	Avoid in infants <3 months, G6PD deficiency, renal failure

as to when to consider stopping prophylaxis. Generally, the risk of scarring following a UTI is reduced after the age of 5 years.<sup>7</sup>

**ANTIBIOTIC PROPHYLAXIS IN SPECIFIC CONDITIONS**

The recommendations by various guidelines for antibiotic prophylaxis in the common clinical indications are given in Table 2.<sup>4,10–13</sup>

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.<sup>14</sup>

**EVIDENCE FOR ANTIBIOTIC PROPHYLAXIS**

The key clinical trials in recurrent UTI and vesicoureteric reflux (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

**Table 2:** Guidelines on antibiotic prophylaxis in specific conditions<sup>4,10–13</sup>

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

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

**Table 3:** Key clinical trials and systematic reviews on antibiotic prophylaxis in children<sup>15–18,20</sup>

Study title	Design	Patient/review characteristics	Follow up	Primary outcome	Secondary outcome/comments
RIVUR	RCT cotrimoxazole vs placebo	603 children with VUR grade I–IV 2–71 months	2 years	Recurrence of UTI reduced by 50% in CAP group	There was no difference in scarring or antibiotic resistance between the groups
PRIVENT	RCT cotrimoxazole vs placebo	780 children <18 years with UTI ± VUR	1 year	Reduction of UTI episodes irrespective of VUR status in CAP group	No difference in renal scarring
Swedish reflux trial	RCT surveillance vs CAP vs endoscopic correction	203 children 1–2 years grade III–IV VUR	2 years	Reduction of UTI in girls on CAP	Scarring was high in the surveillance group
Role of antibiotic prophylaxis in AHN	Systematic review from EAU	57 articles (only 2 RCTS)		Reduction of UTI in <ul style="list-style-type: none"> <li>• Uncircumcised boys</li> <li>• Ureteral dilatation</li> <li>• Higher grades of HN</li> </ul>	Heterogeneity of the ANH group and low-quality evidence were the drawbacks
Long-term antibiotics for preventing recurrent UTI	Cochrane systematic review 2019	16 studies		Modest reduction of UTI	Evidence regarding antibiotic resistance was inconclusive

RIVUR, randomized intervention for children with VUR; RCT, randomized controlled trial; CAP, continuous antibiotic prophylaxis; PRIVENT, prevention of recurrent UTI in children with VUR and normal urinary tracts; AHN, antenatal hydronephrosis; UTI, urinary tract infection

was no significant reduction in the prevalence of renal scarring.<sup>15–17</sup> 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.<sup>18</sup>

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.<sup>19</sup>

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, ureteric dilatation and in male children who are uncircumcised.<sup>20</sup> 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.<sup>21</sup>

## 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.

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