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Review – Infections

Urinary Tract Infection in Children: Management in the Era of Antibiotic Resistance—A Pediatric Urologist's View

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Abstract

Context: Antibiotic resistance to uropathogens has grown significantly worldwide. Today, pediatric urologist experience a situation that needs appropriate action because urinary tract infections are one of the most common bacterial infections in children. **Objective:** In this overview we aimed at presenting the clinical aspects of antibiotic usage in pediatric urology. Our intention was to take part of the important debate regarding future management of bacterial resistance against antibiotics.

Evidence acquisition: We searched PubMed for the terms: [UTI in children], [Recurrent UTI in children], and [Antibiotic resistance in UTI]. When using these terms, we found a numerous amount (3875) of published clinical articles related to the topic. By means of an overview, we chose not to focus on a specific condition but to an overall understanding of the problems related to pediatric urology in general.

Evidence synthesis: We found that usage of antibiotics has had an unquestionable benefit to reduce the morbidity and mortality related to urinary tract infections in childhood. However, recent studies suggest that early exposure to antibiotics in childhood might have negative systemic effects related to neurocognitive function, body metabolism, and fat distribution. In addition to increased resistance to common antimicrobial agents, it has resulted in increased costs and inadequate effect in severe infections. This calls for changes in the clinical management of urinary pathogens in pediatric urology.

Conclusions: As the prevalence of antibiotic resistance grows, pediatric urologists have a key role in managing its consequences and its prevention.

Patient summary: In this overview we looked at the consequences of antibiotic usage treating urinary tract infections in childhood. We found that the prevalence of antibiotic resistance has grown. We concluded that decision-makers must know about the short-and long-term effects of antibiotic usage in children. When we understand the development of antibiotic resistance better, we can build up prevention strategies.

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1. Introduction

Urinary tract infections (UTI) are one of the most common bacterial infections in children and a major cause of

hospitalization [1]. Susceptibility to UTIs in small children has been attributed to several causes, for example, changes in bacterial gut flora, immature immune system, and urinary tract anomalies, among which vesicoureteral reflux

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Table 1 – Table summarizing the current recommendations of antibiotic use according to the European Association of Urology and European Society for Pediatric Urology guidelines [6].

Diagnosis	Recommendation
Hypospadias	Prophylactic antibiotics during surgery.
UTI	Based on local antimicrobial sensitivity patterns and should later be adjusted to sensitivity testing of the isolated uropathogen.
	Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage.
Neurogenic bladder	Patients with VUR should usually be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage.
Megaureter (primary)	Low dose prophylactic antibiotics within the 1st yr of life are recommended for the prevention of UTIs, although there are no existing prospective randomized trials evaluating the benefit of this regimen.
VUR	Regardless of the grade of the reflux or presence of renal scars, all patients diagnosed within the 1st yr of life should be treated initially with continuous antibiotic prophylaxis.
	In all children presenting at age 1–5 yr, continuous antibiotic prophylaxis is the preferred option for initial therapy. For those with high-grade reflux or abnormal renal parenchyma, surgical repair is a reasonable alternative. In patients with lower grades of reflux and without symptoms, close surveillance without antibiotic prophylaxis may be an option.
Ureterocele	When the diagnosis is made by ultrasound, prophylactic antibiotic treatment is indicated until a VCUG can be performed.
	In a clinically asymptomatic child with a ureterocele and a nonfunctional or hypofunctional upper pole, without significant obstruction of the lower pole, and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated.
Posterior urethral valves	During the 1st mo of life, antibiotic prophylaxis may be given especially in those with high-grade reflux.
UTI = urinary tract infection; VCUG = voiding cystourethrogram; VUR = vesicoureteral reflux.	

(VUR) is the most frequent [2]. Prompt diagnosis and treatment are crucial for appropriate outcome and prevention of long-term morbidity associated with renal scaring such as hypertension, toxemia in pregnancy, development of chronic kidney disease, and ultimately the need of renal transplantation [1]. In the preantibiotic era, UTI had a mortality rate as high as 20% [3]. The early treatment of UTI decreases the rate of morbidity, implying that in most cases antimicrobial therapy could be prescribed empirically [4]. However, the pediatric urological community is now confronting a growing concern about the antibiotic resistance of urinary pathogens due to improper and extensive use of antibiotics.

In an effort to reduce renal damage as a result of VUR, various forms of surgical repair of the vesicoureteral junction have been performed [5]. The use of antibiotic prophylaxis to protect children with VUR from UTIs emerged as a response to the recognition of the strong association between UTIs and VUR [5]. Eventually antibiotic prophylaxis was established as the standard treatment for children with VUR [5]. Over time, its use was extended to other indications such as UTI without VUR, hydronephrosis, posterior urethral valves, or neurogenic bladder dysfunction [5]. Table 1 shows the current guidelines for prophylactic and therapeutic use of antibiotic in pediatric patients, by the European Association of Urology/European Society for Pediatric Urology [6]. However, in some cases there is a lack of controlled studies to support the use of prophylaxis, although it has become common practice to prescribe prophylaxis to many children, often for several years [5].

2. Evidence acquisition

2.1. Microorganisms and antibiotics for prophylaxis in childhood UTI

In childhood, *Escherchia coli* is the predominant pathogen found in 90% of girls and in 80% of boys in primary UTIs

[5]. The different bacterial spectrum between boys and girls in UTIs has been explained by anatomical differences and related due to the natural colonization of the preputial area in uncircumcised boys with non-*E. coli* Gram-negative bacteria. An important susceptibility factor responsible for the predominance of *E. coli* is its ability to attach to the urinary tract urothelium. In recurrent UTI, non-*E.coli* organisms such as: *Klebsiella*, *Enterococci*, *Enterobacteriaceae*, and *Proteus*, are identified more frequently. Atypical species are also more commonly seen in infections secondary to invasive procedures or indwelling catheters. UTIs following antibiotic treatment for other infections is also more frequently caused by non-*E. coli* species as repeated antibiotic treatment favors and selects atypical pathogens.

The commonly used prophylactic antibiotic, trimethoprim, has good bioavailability and attains high concentrations in the urine. It is usually well-tolerated by children and easy to administer by its soluble oral preparation. It has been shown that in combination with sulfamethoxazole, it eliminates periurethral *E. coli*, leaving the anaerobic microflora intact [7]. Nowadays, the main concern with trimethoprim, alone or combined with sulfamethoxazole, is the common selection of resistant strains [5]. The prevalence of *E. coli* resistance to trimethoprim is now so high (ranging from 15% to 85% of *E. coli* isolates) [8–11] that this agent, in most countries, is no longer appropriate for empiric treatment of UTIs in children [2].

Nitrofurantoin is absorbed completely in the proximal intestine and has a low impact on the commensal large intestinal flora. It is eliminated by the kidneys and concentrated in the urine. In spite of its widespread use, selection of resistant bacteria is still unusual. Nitrofurantoin, in contrast to trimethoprim, is rapidly excreted, and omitting one or two doses may be sufficient for recurrences to occur [5].

Other antimicrobials such as ampicillin or amoxicillin cannot be used for the empiric treatment in childhood UTI because resistance to these agents has been found in up to 46% of *E. coli* isolates from children with UTIs [5].

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