# Antibiotic resistance in pediatric urology

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***Abstract*:** Antibiotics are a mainstay in the treatment of bacterial infections, though their use is a primary risk factor for the development of antibiotic resistance. Antibiotic resistance is a growing problem in pediatric urology as demonstrated by increased uropathogen resistance. Lack of urine testing, nonselective use of prophylaxis, and poor empiric prescribing practices exacerbate this problem. This article reviews antibiotic utilization in pediatric urology with emphasis on modifiable practice patterns to potentially help mitigate the growing rates of antibiotic resistance. This includes urine testing to only treat when indicated and tailor broad-spectrum therapy as able; selective application of antibiotic prophylaxis to patients with high-grade vesicoureteral reflux and hydronephrosis with counseling regarding the importance of compliance; and using local antiobiograms, particularly pediatric-specific antiobiograms, with inpatient *versus* outpatient data.

***Keywords:*** urinary tract infections, antibiotic resistance, pediatrics, antibiotic prophylaxis, antibiogram, patient compliance, treatment outcome

## Introduction

Antibiotics are a mainstay in the treatment of bacterial infections. Appropriate prescribing is essential to improve patient outcomes and to help prevent the emergence of resistant organisms [Erb *et al.* 2007; Boggan *et al.* 2012]. Antibiotic consumption is suggested to be a primary risk factor for the development of antibiotic resistance. Although there has been a decrease in overall use of antibiotics in the United States by 17% in the last decade, there is still evidence of antibiotic overuse and misuse [The Center for Disease Dynamics, Economics and Policy, 2013]. These factors contribute to antibiotic resistance, which is not only a growing problem in medicine in general, but also in pediatric urology specifically. This article reviews antibiotic utilization in pediatric urology with an emphasis on modifiable practice patterns to potentially help mitigate the growing rates of antibiotic resistance.

## Resistance

### *A brief history*

The cycle of bacterial resistance has plagued antibiotic efficacy since the beginning of antibiotic use. Often, it is a progression from antibiotic discovery to the emergence of antibiotic resistance. This leads to the investigation and uncovering of the resistance mechanism with subsequent antibiotic modification to overcome the resistance mechanism. For example, the discovery of penicillin in 1928 was shortly followed by the identification of a bacterial penicillinase in 1940, several years *before* penicillin's introduction as a therapeutic. As a result, penicillin was synthetically modified to prevent cleavage by penicillinases. This example typifies the history of antimicrobials and the development of resistance, which hinders their therapeutic use and can ultimately lead to multidrug-resistant bacterial pathogens [Austin *et al.* 1999; Levy, 2001; Lieberman, 2003; Davies and Davies, 2010].

Excessive use of antibiotics compounded by the paucity of new agents on the market has led to antibiotic resistance compromising the efficacy of these medications [De Man *et al.* 2000; Singer *et al.* 2003; Bartoloni *et al.* 2004; Erb *et al.* 2007; Davies and Davies, 2010]. Costelloe and colleagues reviewed literature describing the effect of antibiotic prescribing patterns in the primary care setting on antimicrobial resistance in individual patients [Costelloe *et al.* 2010]. They found that individuals prescribed antibiotics consistently had bacteria in the urinary tract resistant to the same antibiotics for up to 12 months. Moreover, the greater the number or duration of antibiotic courses prescribed in the previous 12 months, the greater the likelihood that resistant bacteria would

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be isolated from that patient. This is now a global public health problem acknowledged by the World Health Organization, which has launched a Global Strategy for Containment of Antimicrobial Resistance [World Health Organization, 2001].

The use of antibiotics in animals used for human consumption, therapeutically, prophylactically, and as growth promoters, also contributes to the increasing rates of resistance. Though, it is unclear what proportion of human resistance is attributable to antibiotics used in livestock [Singer et al. 2003], Bartoloni and colleagues studied a remote Bolivian community without human, veterinary, or agriculture antibiotic use. They found 67% of subjects were carriers of *Escherichia coli* with acquired resistance, suggesting an efficient spread of resistant strains even without antimicrobial consumption, perhaps facilitated by unhygienic conditions [Bartoloni *et al.* 2004].

As the dilemma of bacterial resistance is now uniformly recognized, there is a growing body of literature addressing this problem. Relevant to pediatric urology, the resistance pattern of uropathogens has been evolving. Compared with the years 2002–2004, in 2009 trimethoprim/sulfamethoxazole (TMP/SMX) resistance rates for *E. coli* pediatric urinary tract infections (UTIs) increased in both boys (from 23% up to 31%) and girls (from 20% up to 23%). There was also a 10-fold increase in *E. coli* resistance to ciprofloxacin in boys (from 1% in 2002–2004 to 10% in 2009) and girls (from 0.6% to 4%) in pediatric UTIs [Gaspari *et al.* 2005; Edlin *et al.* 2013]. Moreover, pediatric hospitalizations for pyelonephritis in California increased 80% from 17 per 100,000 children in the population in 1985 to 31 per 100,000 in 2006, despite the fact that outpatient management is well supported in the literature [Copp *et al.* 2011]. Among these pyelonephritis admissions, there was a fivefold increase in resistant uropathogens.

### *Antibiotic use*

Consumption of antibiotics for human therapy is generally recognized as a primary driver of resistance patterns. There is a well established temporal relationship between antibiotic use and resistance within the hospital [López-Lozano *et al.* 2000] as well as at the community level [Gottesman *et al.* 2009]. Sun and colleagues described a seasonal effect of antibiotic use on antibiotic resistance [Sun *et al.* 2012]. They demonstrated a significant correlation between antibiotic prescriptions for aminopenicillins and fluoroquinolones and a 1-month lag in *E. coli* resistance prevalence. Antibiotic prescribing patterns specifically influence uropathogen resistance levels in children as well. Paschke and colleagues evaluated over 500 children who presented with a first UTI and had antibiotics exposure in the preceding 120 days [Paschke *et al.* 2010]. They demonstrated a fourfold increase in the odds of resistance to ampicillin and amoxicillin clavulanante following amoxicillin exposure within 30 days prior to the UTI.

It is evident that failure to address antibiotic resistance will lead to the development of increasing resistance. The reversibility of this effect has also been investigated. Austin and colleagues used population genetic methods and epidemiological observations and showed that the time scale for emergence of resistance under constant selective pressure is much shorter than the decay time after cessation or decline in the level of drug use, necessitating early intervention once resistance is detected [Austin *et al.* 1999]. Interestingly, Nasrin and colleagues studied the effect of β-lactam antibiotic use in children on pneumococcal resistance to penicillin and suggested that the reduction of antibiotics could result in a rapid drop of resistance rates (about 6 months) [Nasrin *et al.* 2002]. Specific to urologic pathology, Gottesman and colleagues conducted a retrospective study and assessed the proportion of quinolone-susceptible *E. coli* surrounding a nationwide ciprofloxacin restriction [Gottesman *et al.* 2009]. They demonstrated a significant decrease in *E. coli* nonsusceptibly to quinolones from 12% to 9%; notably, this was reversed immediately when quinolone consumption rose.

### *Antibiotic misuse*

There is evidence that physicians are potentially misusing certain antibiotics in the outpatient treatment of pediatric UTIs. Although the number of prescriptions per capita has decreased, there has been a shift towards using newer, more powerful antibiotic classes, including macrolides and fluoroquinolones. According to the Center for Disease Dynamics, there were fewer overall prescriptions for antibiotics in 2010 *versus* 1999, but the prescription of macrolides increased from 22% to 27%; similarly, the prescription of quinolones increased from 9% to 12% [The Center for Disease Dynamics, Economics and Policy, 2013] Increased use of a single antibiotic or antibiotic class can accelerate the rise of bacterial resistance.

Ineffective empiric antibiotic therapy may contribute to increased morbidity and increased costs due to prolonged antibiotic treatment, recurrent office or emergency room visits, and hospital admissions [Yen *et al.* 2003]. In 2010, the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases updated the practice guidelines for uncomplicated UTIs [Gupta *et al.* 2011]. Based on expert opinion derived from clinical, *in vitro*, and mathematical modeling studies, TMP/SMX should not be used empirically if local resistance rates of uropathogens exceed 20%. However, data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey suggest that 50% of children were prescribed TMP/SMX for UTIs despite the fact that most regions in the USA have resistance rates to TMP/SMX that exceed the recommended level for empiric prescribing of this antibiotic [Copp *et al.* 2011]. In addition, 32% of children with UTIs were treated with a broad-spectrum antibiotic. Recent examination of national UTI resistance patterns has demonstrated that most UTIs are sensitive to narrow-spectrum alternatives, such as first-generation cephalosporins and urinary anti-infectives (nitrofurantoin) [Edlin *et al.* 2013]. These underutilized classes of antibiotics have demonstrated consistently low resistance rates over time.

### *Antibiotic overuse*

Lastly, there is evidence for overuse of antibiotics in the pediatric urology community. Febrile UTI is one of the most common serious bacterial infections in childhood because of the potential associated renal scarring [Montini *et al.* 2007] with permanent renal damage in about 5% [Coulthard *et al.* 1997] that may lead to hypertension, proteinuria, and hyposthenuria among other consequences [Jacobson *et al.* 1989]. As the frequency of reinfection may be up to 30% [Winberg *et al.* 1975], it became common practice to prescribe daily low-dose antibiotic prophylaxis to prevent further UTIs and renal damage in children with risk factors for recurrent infections, including vesicoureteral reflux (VUR) and prenatal hydronephrosis.

Until recently, this practice has gone unquestioned. Active treatment to prevent UTIs and renal damage has been considered so apparent that for ethical reasons a control group without preventive measures has not been included in studies until the last decade [Braga *et al.* 2013]. In 2010, a Cochrane Review addressed the efficacy and harms of long-term antibiotics to prevent recurrent UTIs in children [Williams and Craig, 2012]. Ultimately, the authors included 12 studies, notably including the PRIVENT Study [Craig *et al.* 2009] and a study by Montini and colleagues [Montini *et al.* 2008] as two large, well reported studies that estimated a risk reduction of approximately 0.65–0.75. Together with the other included studies, the Cochrane Review concluded that long-term antibiotics appear to reduce the risk of repeat symptomatic UTIs in susceptible children, but the benefit is small, about 8%, corresponding to the need to treat 12 or 13 children for 12 months to prevent one UTI. This must be considered together with the increased risk of microbial resistance as the data also suggested that prolonged administration results in changes in uropathogen susceptibility with an increased risk of symptomatic UTIs caused by bacteria resistant to the prophylactic agent [Conway *et al.* 2007; Cheng *et al.* 2008; Craig *et al.* 2009; Braga *et al.* 2013]. Conway and colleagues reviewed over 600 children with first UTI and 83 with recurrent UTI and found not only that antibiotic prophylaxis was not associated with decreased risk of recurrent UTI [hazard ratio (HR) 1.01], but also that prophylaxis was a risk factor for antimicrobial resistance (HR 7.50) [Conway *et al.* 2007].

Importantly, there is also evidence that the choice of antibiotic for prophylaxis is relevant. Cheng and colleagues examined bacterial antimicrobial resistance of recurrent UTIs in over 300 children receiving antibiotic prophylaxis because of VUR and found that children receiving cephalosporin prophylaxis are more likely to have extended-spectrum β-lactamase-producing bacteria or multidrug-resistant uropathogens for breakthrough UTIs; therefore, they suggest these antibiotics are not appropriate for prophylactic use in patients with VUR [Cheng *et al.* 2008].

*Vesicoureteral reflux.* VUR has historically been managed with antibiotic prophylaxis due to the concern for increased risk of repeated pyelonephritis [Wald, 2004]. However, there have been a number of recent studies evaluating the validity of this recommendation.

Some randomized, controlled trials demonstrate no benefit from antibiotic prophylaxis. Conway and colleagues found no significantly increased

risk of UTI recurrence for children with grade I–III VUR and that, in this population, continuous antibiotic prophylaxis had no significant effect on risk of UTI recurrence [Conway *et al.* 2007]. Similarly, Garin, and Roussey-Kesler and colleagues each studied over 200 patients with grade 0–III VUR and concluded that there was no support for antibiotic prophylaxis to prevent febrile UTIs in low-grade reflux [Garin, 2006; Roussey-Kesler *et al.* 2008]. Furthermore, Montini and colleagues evaluated over 300 children with no or grade I–III VUR and found no difference in the number of febrile recurrences [Montini *et al.* 2008].

A careful analysis of these studies reveals that it is primarily in patients with low-grade VUR that there is no benefit. There does appear to be value from antibiotic prophylaxis in enrolled patients with higher grades of VUR as these patients do have an increased rate of UTI as well as pyelonephritis and renal scarring. Conway and colleagues report an increased risk of UTI recurrence with grades IV and V (HR 4.38), though this study was not powered to determine the effect of prophylaxis on risk of UTI recurrence in children with grade IV–V VUR [Conway *et al.* 2007]. Roussey-Kesler and colleagues found that prophylaxis significantly reduced UTIs in boys with grade III VUR [Roussey-Kesler *et al.* 2008]. To our knowledge, there have been very few studies focusing on patients with high-grade VUR. The Swedish Reflux Trial in Children evaluated 200 children aged 1–2 years with grades III and IV reflux and concluded that prophylaxis decreased the febrile UTI rate in girls, though not in boys [Brandström *et al.* 2010]. While this trial was not able to conclude a decreased febrile UTI rate in boys, this may be a consequence of the low baseline risk for UTI in boys older than 1 year. In contrast, a smaller randomized study by Pennesi and colleagues included 100 children with grade IV reflux and found no difference in the number of patients with recurrent febrile UTI regardless of VUR grade or gender [Pennesi *et al.* 2008]. Interestingly, the patients in this study were evaluated though repeated cystourethrographies, renal ultrasounds, and dimercaptosuccinic acid scans and the presence of renal scars was the same in children with and without antibiotic prophylaxis.

These studies suggest that antibiotic prophylaxis for patients with low-grade reflux does not have a significant impact on reducing UTI recurrence, and in fact, may cause an increase in resistant uropathogens. Therefore, based on the current literature, it is appropriate and reasonable to avoid prophylaxis in patients with low-grade VUR. However, for those with high-grade reflux, the current evidence suggests that prophylaxis may be beneficial, though more randomized, controlled trials focusing on patients with high-grade reflux will continue to refine the optimal management of these patients.

*Hydronephrosis.* Antenatal hydronephrosis is one of the most common anomalies detected on prenatal ultrasonography, reported in approximately 1–5% of all pregnancies [Nguyen *et al.* 2010]. Postnatal treatment with daily oral antibiotic prophylaxis had been recommended to reduce the rate of UTIs [Woodward and Frank, 2002], though there has been a paucity of high-level data defining the relationship between nonrefluxing antenatal hydronephrosis and the risk of UTI.

Braga and colleagues performed a meta-analysis to determine the value of antibiotic prophylaxis in reducing the rate of UTIs in this patient population [Braga *et al.* 2013]. They included 21 studies of children with antenatal hydronephrosis and concluded that children with high-grade prenatal hydronephrosis may benefit from prophylaxis with a reduced UTI rate on prophylaxis, 14.6% *versus* 28.9% without prophylaxis. In contrast, there does not appear to be a clinically significant impact on UTI rate with prophylaxis for those with low-grade prenatal hydronephrosis, 2.2% with prophylaxis *versus* 2.8% without prophylaxis. However, the publications contributing to this review recognized shortcomings, including limited number of patients, event monitoring, and compliance assessment. Of note, 16 studies did include patients with VUR, prevalence ranging from 1.8% to 100%, though the VUR grade was not identified. Due to the paucity of data, the impact of important variables such as sex, VUR, and circumcision status could not be assessed and more studies would be valuable in continuing to tailor recommendations of patients with antenatal hydronephrosis. That said, based on the current literature, it is appropriate and reasonable to avoid prophylaxis in patients with low-grade hydronephrosis.

*Compliance.* Further complicating the matter is evidence that compliance with antibiotic prophylaxis is poor and that poor compliance may also lead to increased risk for antibiotic resistance [Tenover and McGowan, 1996; Bollgren, 1999;

Koyle and Caldamone, 2007]. Using a large pharmacy claims database, it was determined that 60% of children with VUR were noncompliant with prophylaxis [Copp *et al.* 2010]. Notably, younger age, hospitalizations, and specialists visits were associated with improved compliance, suggesting that compliance may be improved through increased patient contact with the healthcare system and by counseling parents and older patients to stress the importance of treatment regimen adherence. Moreover, this information is critical as future investigations in the usefulness of antimicrobial prophylaxis are considered; if compliance is only 40%, it becomes more difficult to interpret the results from these studies.

## Improving antibiotic prescribing patterns

Changing these trends in resistance patterns is complex as resistance is not solely due to the therapeutic and prophylactic use of antibiotics in humans [Davies and Davies, 2010]; however, changes in antibiotic prescribing patterns may be the most easily altered. Combating misuse and overuse of antibiotics in the treatment of UTIs can begin by carefully considering which patients are placed on prophylaxis. This management option should only be provided to those patients at highest risk for UTIs and greatest likelihood for clinical benefit from prophylaxis. Current evidence suggests this includes patients with high-grade VUR or high-grade antenatal hydronephrosis. For those who are treated with antibiotic prophylaxis, cephalosporins are not recommend due to their association with the development of uropathogen resistance as discussed above [Cheng *et al.* 2008]. If antibiotic prophylaxis is used, families may benefit from directed counseling regarding the importance of compliance to help prevent resistance.

Next, the use of confirmatory urine testing should be performed. Urine culture results allow for tailoring of broad-spectrum therapy and provide the opportunity to stop empiric therapy if there is no bacterial growth. However, a recent study demonstrated approximately one-third of children under 2 years of age did not have any urine testing (either urinalysis or culture) performed in the setting of antibiotic-treated UTIs [Copp *et al.* 2013]. Of note, urologists had 50% lower odds of urine culture use among antibiotic-treated UTI episodes compared with internists/family medicine physicians. This is in clear contravention to the American Academy of Pediatrics guidelines for UTI management that recommend obtaining a urine specimen for both urinalysis and culture if a clinician treats a febrile infant with no apparent source of fever [Subcommittee on Urinary Tract Infection, 2011]. At the very least, populations at higher risk for uropathogen resistance, including those with history of prior UTIs [Sotto *et al.* 2001; Cheng *et al.* 2008], recent antibiotic exposure [Allen *et al.* 1999; Cheng *et al.* 2008], or presence of genitourinary anomaly [Allen *et al.* 1999; Cheng *et al.* 2008] should undergo urine testing in conjunction with empiric treatment.

As the above evidence suggests, prescribing patterns do not match resistance patterns. Rising resistance rates may be curbed by improving empiric prescribing patterns through the use of local antibiograms, which are published by 98% of US hospitals surveyed [Ernst *et al.* 2004]. In this manner, empiric antibiotic therapy can be appropriately selected without unnecessarily overusing broad-spectrum antibiotics. Though, these must be tailored to the population being treated. Boggan and colleagues demonstrated that susceptibility patterns may vary significantly by age [Boggan *et al.* 2012]. While no additional resources are required to separate results based on patient age, hospitals often combine susceptibility data for adults and children. Dahle and colleagues demonstrated differences between inpatient and outpatient resistance patterns and recommended separate antibiograms by visit setting [Dahle *et al.* 2012]. In a recent study (unpublished data), inpatient and outpatient urinary isolates from children under 18 years were examined using The Surveillance Network, and compared 25,418 outpatient and 5560 inpatient urinary isolates. This revealed that uropathogen resistance for many antibiotics was higher in the inpatient setting. For example, for *E. coli* (the most common uropathogen overall): TMP/SMX resistance was 30% for inpatients *versus* 24% for outpatients and cephalothin resistance was 22% for inpatients *versus* 16% for outpatients ($p < 0.001$). This further emphasizes the value of separate hospital- and community-based antibiograms in order to optimize empiric prescribing for pediatric UTIs.

## Conclusion

Antibiotic resistance is a growing problem in pediatric urology as highlighted by the significantly increased uropathogen resistance to TMP/SMX and ciprofloxacin. Poor empiric

prescribing practices, lack of urine testing, and nonselective use of prophylaxis exacerbate this problem. However, three small changes in practice patterns may curb the growing resistance rates: use of urine testing in order to only treat when indicated and tailor broad-spectrum therapy as able; selective application of antibiotic prophylaxis to patients with high-grade VUR and high-grade hydronephrosis with counseling regarding the importance of compliance; and use of local antiobiograms, particularly pediatric-specific antiobiograms, with inpatient *versus* outpatient data.

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## Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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