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ANTIBIOTIC RESISTANCE IN CHILDREN

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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

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.

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.

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 .

Costelloe and colleagues reviewed literature describing the effect of antibiotic prescribing patterns in the primary care setting on antimicrobial resistance in individual patients.

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

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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%).

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. 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 as well as at the community level. Sun and colleagues described a seasonal effect of antibiotic use on antibiotic resistance. 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 . 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. 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).. 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. 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 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 with permanent renal damage in about 5% that may lead to hypertension, proteinuria, and hyposthenuria among other consequences

As the frequency of reinfection may be up to 30% ,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. In 2010, a Cochrane Review addressed the efficacy and harms of long-term antibiotics to prevent recurrent UTIs in children. Ultimately, the authors included 12 studies, notably including the PRIVENT Study and a study by Montini and colleagues 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 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)

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 Using a large pharmacy claims database, it was determined that 60% of children with VUR were noncompliant with prophylaxis. 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 however, changes in antibiotic prescribing patterns may be the most easily altered. Combating misuse and overuse of antibiotics in the treatment 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.

Parents play a big role in stopping antibiotic misuse and the public health crisis that can result. To help prevent antibiotic resistance, follow these guidelines when your child is ill:

- Don’t demand antibiotics when a health care provider has determined they’re not needed
- Talk about antibiotic resistance with your child’s doctor
- If your child is prescribed an antibiotic for a bacterial infection, be sure he/she takes the medications as prescribed, even if symptoms disappear. If treatment stops too

soon, some
bacteria may survive and become more difficult to treat in the future

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;

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