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Review Article

Antibiotic Resistance Patterns of Urinary Tract Pathogens in Children: Current Clinical Challenges and Therapeutic Perspectives

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Abstract

Urinary tract infections (UTIs) are common infections among children and are the most common proven bacterial infection in febrile infants without localising signs. UTIs are commonly caused by anatomical or functional abnormalities in the kidney and urinary tract The effective management of urinary tract infections has become increasingly difficult due to significant resistance to frequently prescribed antibiotics, such as amino-penicillins, and the rising global prevalence of multi-drug-resistant organisms responsible for these infections.

Keywords: *Urinary Tract Infections; Children; Newborn; Fever; Renal Scarring; Posterior Urethral Valves; Multidrug Resistance; Escherichia coli; Klebsiella pneumoniae; Extended-Spectrum B-Lactamases; Penicillin; Carbapenems*

Abbreviations

UTI: Urinary Tract Infections; VUR: Posterior Urethral Valve; NB: Neurogenic Bladder; UPJO: Ureteropelvic Junction Obstruction; CAKUT: Congenital Abnormalities of the Kidney and Urinary Tract; MDR: Multidrug Resistance; ESBLs: Extended-Spectrum β-Lactamases; TMP-SMX: Trimethoprim-Sulfamethoxazole; ESBL-PE: ESBL-Producing *Enterobacteriaceae*; *E. coli*: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneumoniae*; *P. mirabilis: Proteus mirabilis;* EKP: *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis*; KPC: *Klebsiella pneumoniae* Carbapenemase; NDM-1: The New Delhi Metallo-Beta-Lactamase-1; MDRO: Multidrug-Resistant Organisms; XDR: Extensively Drug Resistant

Introduction

Urinary tract infections (UTIs) are common infections among children and are the most common proven bacterial infection in febrile infants without localising signs [1]. It has been estimated that the overall prevalence of childhood UTI is 7.0% and 7.8%, respectively, in infants and children presenting to health services with fever and/or other symptoms of UTI [2]. The incidence varies with age and sex. The incidence for boys is highest during the first 6 months of life (5.3%) and decreases with age to around 2% for the ages 1 - 6 years. In girls the incidence is reversed with UTIs being less common during the first 6 months (2%) and increasing with age to around 11% for the ages of 1 - 6 years [3].

UTI is an infection caused by the spread and growth of uropathogens, as a result of the ascent of bacteria from the urethra and hematogenous spread of bacteria. The short-term symptoms include fever, urinary frequency, dysuria with or without frequency, urgency, haematuria and suprapubic pain [4]. If not treated properly, it often develops health problem worldwide including recurrent UTI, renal scarring, even damage of renal function, particularly in infants less than 2 months of age [5].

Risk factors for UTI

UTIs are commonly caused by anatomical or functional abnormalities in the kidney and urinary tract. It has been reported that these anomalies were investigated in 30% of neonates during their first UTI episode, including 47% of febrile newborns [6,7]. The most prevalent defects included vesicoureteric reflux (VUR), a duplicated collecting system, posterior urethral valves (PUV), neurogenic bladder (NB), ureteral obstruction, and ureteropelvic junction obstruction (UPJO). UTIs with congenital abnormalities of the kidney and urinary tract (CAKUT) are called complex UTIs. UTIs in childhood are frequently used to eliminate the bacterial pathogen, identify CAKUT, and prevent recurrent infections [8].

Approximately 85% to 90% of UTIs are caused by *Escherichia coli*. Other common organisms include *Klebsiella, Proteus, Enterococcus*, and *Enterobacter* species [9,10]. Organisms such as *Pseudomonas*, group B *Streptococcus*, and *Staphylococcus aureus* are usually associated with CAKUT, genitourinary surgery, a foreign body (e.g. catheter), or recent antibiotic treatment, whereas infection with urea-splitting organisms (e.g. *Proteus*) is associated with stone formation [11].

Mechanism of multidrug resistance (MDR)

The effective management of urinary tract infections has become increasingly difficult due to significant resistance to frequently prescribed antibiotics, such as amino-penicillins, and the rising global prevalence of multi-drug-resistant organisms responsible for these infections [12]. Extended-spectrum β-lactamases (ESBLs) represent a specific category of β-lactamase that hydrolyses and contributes to resistance against a range of β-lactam antibiotics, such as third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) and monobactams (aztreonam), while showing no activity against cephamycins or carbapenems. These enzymes are predominantly produced by *Enterobacteriaceae* [13]. A majority of ESBLs are carried by extensive plasmids, facilitating their dissemination across various bacterial genera while containing numerous co-resistance genes, including those responsible for aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole (TMP-SMX) [13,14].

The emergence of ESBL-producing *Enterobacteriaceae* (ESBL-PE), primarily *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), and *Proteus mirabilis* (*P. mirabilis*) (EKP), has spread in community and hospital settings worldwide [15]. Currently, carbapenems remain the treatment of choice for severe pediatric ESBL infections due to their reliability. However, resistance has ensued posing an issue of reserving carbapenems for more serious infections and finding alternative antibiotics for ESBL-producing-EKP UTI, including amikacin and β-lactam-β-lactamase inhibitor [16].

Another class of beta-lactamases known as carbapenems hydrolyses carbapenems as well [17]. The *Klebsiella pneumoniae* carbapenemase (KPC) [18] and the New Delhi metallo-beta-lactamase-1 (NDM-1) [19] are two kinds of carbapenemase that are particularly important on a worldwide scale. While most NDM-1 producers do not develop resistance to colistin, they do exhibit wide drug resistance [17]. Because different carbapenemase-producing bacteria are sensitive to older and newer medicines, there is no one-size-fits-all approach to treating this type of infection. As an example, it is common for NDM producers to possess pan-resistance to aminoglycosides [20]. Bacterial development of aminoglycoside-modifying enzymes reduces the drug's binding capacity and is the principal cause of aminoglycoside resistance in *Enterobacterales* [21]. There are a few different ways that bacteria can develop resistance to quinolones. One way is through chromosomal mutations in genes like DNA gyrase and topoisomerase. Another way is by plasmid-mediated resistance, which can be caused by variations in enzymes like AAC or efflux pumps like QepA and OqxAB [22,23].

Prevalence of MDRO colonisation and UTI

There are a number of case-control studies regarding risk factors for UTIs with antibiotic-resistant organisms in children [24-26]. The most frequently cited risk factors are previous antibiotic use, underlying urinary tract anomalies and previous hospitalisation. However, community-acquired multidrug-resistant organisms (MDRO) infection may occur in children without any identifiable risk factors, depending to some extent on the prevalence of ESBL colonisation in the general community [27].

A retrospective study revealed an increasing trend of antimicrobial resistance in uropathogens among children hospitalized for urinary tract infections in Italy, highlighting a notable prevalence of ESBL and multidrug-resistant strains. Previous antibiotic administration, including for urinary tract infection prophylaxis, is associated with antibiotic resistance. Factors contributing to empirical treatment failure encompassed the presence of ESBL or multidrug-resistant uropathogens, a history of recurrent urinary tract infections, antibiotic therapy within the prior 30 days, and empirical treatment utilizing amoxicillin or amoxicillin/clavulanate. In contrast, empirical treatment utilizing third-generation cephalosporins was associated with enhanced outcomes [28].

In children the majority of uropathogens in numerous additional studies were either extensively drug resistant (XDR) or multidrug resistant (MDR) organisms. A study conducted in Australia found that 308 (14.0%) of the 2202 UTIs caused by gram-negative organisms were caused by MDR strains. Approximately 50% of the tested bacteria were resistant to gentamicin, cephalexin, and ceftriaxone, while all of them were resistant to ampicillin and over 80% to trimethoprim. Moreover 20% of the cases showed continued efficacy with the amoxicillin/clavulanic acid combination [26].

480 (64.9%) of the 739 *E. coli* isolates in Nepal [29] were MDR, and 37 (5.0%) were XDR. MDR strains exhibited resistance to ciprofloxacin, ampicillin, amoxicillin/clavulanate, and cephalexin in 80.6%, 81.6%, 84.7%, and 100% of the cases, respectively. MDR *Escherichia coli* isolates were still susceptible to piperacillin/tazobactam (81%), imipenem (92%), and amikacin (87%). The only antibiotics that the XDR isolates were completely resistant to were tigecycline and colistin, which worked well against every pathogen that was tested. Antimicrobial-resistant uropathogens were responsible for 840/1801 cases (46.7%) in a retrospective 8-year study of children hospitalized for UTI in the Emilia-Romagna Region, Italy: 83 (4.7%) were caused by ESBL, 119 (6.7%) by MDR, and 4 (0.2%) by XDR bacteria [28]. *Proteus mirabilis* (6/119, 5.0%), *P. aeruginosa* (12/119, 10.1%), *K. pneumoniae* (7/119, 5.9%), and *E. coli* (62/83, 74.7%) were the most common MDR pathogens, while *K. pneumoniae* (10/83, 12.0%) and *E. coli* (68/119, 57.1%) were the most common ESBL pathogens. *K. pneumoniae* (1/4), and *E. coli* (3/4), were the XDR pathogens. A significant correlation was found between treatment failure and the presence of MDR/XDR or ESBL uropathogens [28].

Management

Empiric treatment of suspected MDR UTI needs to be informed by local antibiotic susceptibility, with rationalisation of antibiotic therapy based on susceptibility results [22]. Some antibiotics used in adults are not approved for use in children [30] or may not be available in a liquid or palatable formulation, posing additional difficulties in this population.

Treatment options also differ according to the mechanism of resistance (Figure 1). Many community-acquired ESBL-producing *Enterobacterales* remain susceptible to oral agents such as fosfomycin and nitrofurantoin. Common intravenous options include carbapenems and aminoglycosides [31]. In severe UTI with or without MDR, initial therapy should, be intravenous. For serious infection with ESBL producers, carbapenems are still commonly recommended as definitive therapy, particularly in cases of severe sepsis or life-threatening situations [20,22].

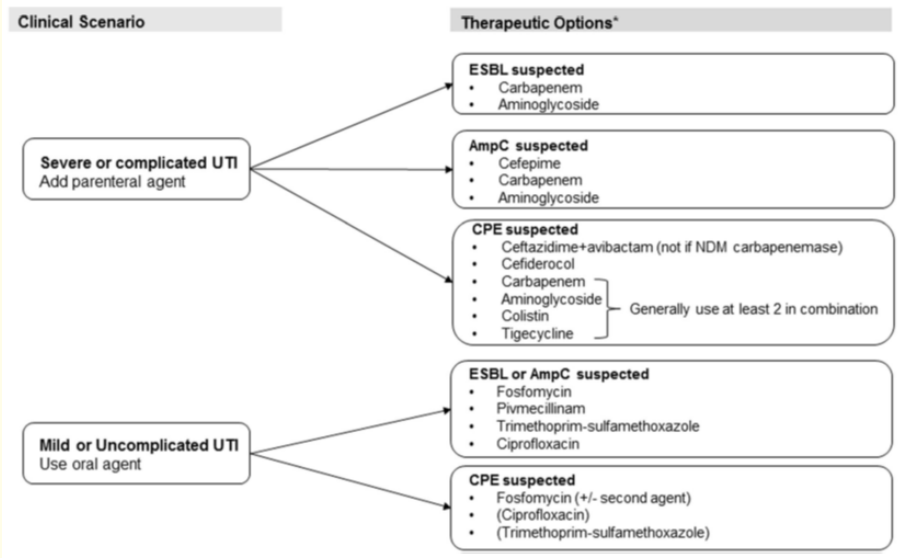

Figure 1: *Mahony, M., McMullan, B., Brown, J. et al. Multidrug-resistant organisms in urinary tract infections in children. Pediatr Nephrol 35, 1563-1573 (2020). https://doi.org/10.1007/s00467-019-04316-5) [27] (Note: Options for empiric treatment of urinary tract infection with high index of suspicion for MDRO. Readers should consult local guidelines, consider local epidemiology/antibiograms where available and modify therapy based on microbiology results and clinical progress, in consultation with infectious diseases/microbiology advice).*

Conclusion and Recommendations

The management of MDRO in UTI in children continues to be a challenge.

In order to optimise efficacy, empiric prescribing guidelines must be customised to the availability of drugs and antibiograms in the local area. While minimising the use of unnecessary broad-spectrum antibiotics, the clinical and microbiological cure is achieved. For this reason, there are no widely accepted guidelines on the management of MDRO UTI in children to date. It is imperative to conduct additional research on antimicrobial agents in children. In particular, agents that have been developed and utilised in adults to treat MDROs must be investigated in order to obtain approval for use in children. infection control programs and antimicrobial stewardship are also essential for reducing the selection pressure of these resistant organisms.

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