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REVIEW

Multidrug-resistant organisms in urinary tract infections in children

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Abstract

The global spread of multidrug-resistant organisms has led to an increase in urinary tract infections (UTIs) in children that are difficult to treat. This review explores the current literature regarding multidrug-resistant UTIs in childhood and proposes an approach to management. Multidrug-resistant organisms include a wide range of potential urinary tract pathogens and, while most literature on drug resistance in UTIs during childhood has focused on extended-spectrum beta-lactamase producing organisms, in this review, we have included a discussion of multidrug resistance including and beyond beta-lactamase production. We provide definitions for multidrug-resistant organisms in line with current consensus guidelines and summarise clinically relevant mechanisms of resistance. Additionally, in this review, we outline the global epidemiology of multidrug-resistant UTIs in children, summarising published prevalence rates, which range from 5 to 90% in different settings. Finally, we also critically review the evidence on risk factors for colonisation and infection of the urinary tract with multidrug-resistant organisms, including prior antibiotic use, hospitalisation and underlying urological malformations. We also highlight multidrug-resistant UTI occurring in children without any identifiable risk factors, reflecting an increasing prevalence of colonisation with these organisms in the general community. Taken as a whole, this emphasises a need for careful and evidence-based use of antibiotics when treating UTIs in children and, to aide clinicians, we have outlined here potential management strategies for when infection with a multidrug-resistant organism is suspected or confirmed.

Keywords Urinary tract infection · Children · Multidrug resistance · Extended-spectrum beta-lactamases

Introduction

Urinary tract infections (UTIs) are common in children. Up to 7% of children will have experienced a UTI by the age of 19 years [1]. The vast majority of UTIs are caused by Gram-negative organisms from the family Enterobacterales (previously called Enterobacteriaceae), of which *Escherichia coli* is the most common, accounting for > 80% of UTIs [2], followed by other Enterobacterales, such as *Klebsiella* spp., *Enterobacter* spp. and *Proteus* spp. Less commonly, other Gram-negative organisms such as *Pseudomonas aeruginosa* may cause UTIs. Potential Gram-positive uropathogens in children include *Enterococcus* spp. and *Staphylococcus saprophyticus* (in adolescents) [3].

The emergence and spread of multidrug-resistant organisms (MDROs, defined below) is a global public health threat [4, 5]. MDROs have become more common in community-acquired infections as well as hospital-acquired infections, though prevalence varies by region [6]. Due to microbial selection pressure, antibiotic resistance follows antibiotic use: In particular, widespread use of cephalosporins and quinolones in humans and animals has been associated with emergence of resistance to these and other antibiotics [1]. Extended-spectrum beta-lactamase (ESBL) enzymes have spread in part due to the transmission of mobile genetic elements between bacteria. In

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addition, clonal expansion of ESBL-producing strains, in particular *E. coli* ST131, which also has high rates of resistance to quinolones, has led to outbreaks globally [7, 8].

Definitions

Multi-drug resistance has been variously described historically: Commonly, MDROs have been described as having in vitro resistance to more than one antimicrobial tested [4], but no formal definitions existed until 2010. International consensus now defines multidrug resistance as non-susceptibility to at least one antimicrobial in three or more classes, based on in vitro antibiotic susceptibility testing [4]. Extensively drug-resistant (XDR) organisms are defined as isolates with susceptibility to only one or two antimicrobial classes, with resistance to agents in all remaining categories [4]. Pan-drug resistance is resistant to all agents in all antimicrobial classes [4].

Most paediatric literature on drug resistance in UTI focuses on ESBLs or other specific resistance mechanisms rather than MDROs as a broad group. While this review discusses MDROs in general, focusing on Gram-negative uropathogens, it will include discussion of ESBLs, given their status in the existing literature and common understanding of 'drug resistance', and the fact that many ESBL-producing organisms have additional resistance mechanisms to other classes. It should be noted, however, that ESBL-producing organisms per se may not meet the international consensus criteria for MDRO. In this review, 'ESBL' generally refers to plasmid-mediated Ambler Class A beta-lactamases, unless otherwise stated (Ambler provides one of several classification systems) [9].

Mechanisms of resistance

There are diverse mechanisms of antimicrobial resistance in Gram-negative organisms (Tables 1 and 2). The most common mechanism in Enterobacterales is the production of beta-lactamases [9]. Beta-lactamases can be classified using various frameworks (Table 1). The Ambler classification system is based on the molecular structure of the enzymes, whereas another commonly used system, the Bush-Jacoby classification, is based on functional characteristics [5]. ESBL producers hydrolyse penicillins, first- to third-generation cephalosporins and aztreonam but may remain susceptible to clavulanic acid combinations (e.g. amoxicillin/clavulanic acid) in vitro [5, 10]. ESBLs are thought to have first arisen from a single nucleotide polymorphism in the *blaSHV* gene, and more than 1600 known ESBLs are in circulation worldwide [11]. Most genes encoding ESBL production are situated on plasmids [5, 12]. Plasmid-mediated resistance is particularly important for public health, as some may be transmissible between different species of Enterobacterales of varying virulence or with pre-existing resistance profiles [5]. Furthermore, ESBL-producing bacteria are often MDROs, as plasmids frequently also carry genes encoding resistance to other antimicrobials, such as aminoglycosides, fluoroquinolones and sulphonamides [7, 13].

Other beta-lactamases have diverse mechanisms of transmission and action. AmpC cephalosporinases can be chromosomally encoded or plasmid-mediated, and are similar to ESBLs in that they hydrolyse penicillins, most cephalosporins and aztreonam, though they are not inhibited by clavulanic acid [5, 11, 14]. Carbapenemases are beta-lactamases that additionally hydrolyse carbapenems [5]. Two carbapenemase types of particular global significance are *Klebsiella pneumoniae* carbapenemase (KPC) [15] and New Delhi metallo-beta-lactamase-1 (NDM-1) [16]. NDM-1 producers have broad drug resistance, though typically remain susceptible to colistin [5]. It is important to remember that carbapenemase-producing bacteria vary in their susceptibility to alternative and newer agents, and thus treatment options differ. For example, NDM producers frequently have pan-resistance to aminoglycosides [17].

Aminoglycoside resistance in Enterobacterales stems mainly from bacterial production of aminoglycoside-modifying enzymes (Table 2), reducing the ability of the drug to bind to the target [3]. Resistance to quinolones can be (1) chromosomal, with point mutations in the DNA gyrase and topoisomerase genes, or (2) plasmid-mediated with pentapeptide repeats in the Qnr proteins, efflux pumps QepA and OqxAB, or a variant of the aminoglycoside-modifying enzyme AAC [13, 18].

Epidemiology

Risk factors for colonisation with MDROs

It is generally accepted that the environment plays a crucial role in the spread of MDROs [19]. Colonisation, which may precede infection, refers to the presence of bacteria (MDROs or otherwise), in the human body, often within the gastrointestinal tract for organisms relevant to this review, which are not causing disease [20]. As most UTIs in children are caused by organisms resident in the gastrointestinal tract, colonisation by multi-resistant bacteria will increase the risk of UTI by MDRO in children who are otherwise predisposed to UTIs. Previous hospitalisation increases the risk of MDRO colonisation [20]. In a prospective study of French children screening for rectal colonisation with an ESBL-producing Enterobacterales, history of hospitalisation within the last 6 months was the only risk factor identified for carriage of an ESBL-producing ST131-*E. coli* strain [7]. When looking at ESBL-producing non-ST131-*E. coli* strains, the same study

Table 1 Ambler classification of selected beta-lactamases

	Enzyme	Example genes	Organisms commonly affected	Notes: implications for detection and treatment
Ambler class A	ESBLs including CTX-M, SHV	$bla_{CTX-M-15}$ $bla_{CTX-M-27}$ $bla_{CTX-M-14}$	*E. coli* *K. pneumoniae* *P. mirabilis*	Inhibited by clavulanic acid Remain susceptible to carbapenems Chromosomal genes may be inducible
	Carbapenemases KPC	*blaKPC*	*E. coli* *K. pneumoniae* *K. oxytoca* *S. marcescens, Enterobacter* spp. *C. freundii*	Inhibited by clavulanic acid
Ambler class B	Metallo-beta-lactamases, including IMP, NDM		*E. coli* *K. pneumoniae* *K. oxytoca* *S. marcescens*, *Enterobacter* spp. *C. freundii*	Remain susceptible to aztreonam NDM producers typically have additional resistance genes
Ambler class C	Cephalosporinases AmpC	bla_{CMY-2}	*Chromosomal AmpC* *Enterobacter* spp. *C. freudii* *S. marcescens* *M. morganii* *P. stuartii* *Plasmid AmpC* *K. pneumoniae* *E. coli*	Chromosomal or plasmid-mediated Chromosomal genes may be inducible Also resistant to aztreonam Remain susceptible to •Carbapenems •4th generation cephalosporins, e.g. cefepime •Avibactam
Ambler class D	Oxacillinases	bla_{OXA-23} bla_{OXA-48} bla_{OXA-1}	*A. baumannii* *P. aeruginosa*	Highly diverse group of enzymes, some also hydrolyse carbapenems

Families of beta-lactamase enzymes: *TEM* named after the first patient Temoniera, *SHV* sulphydryl variable, *CTX-M* named as resistance to cefotaxime, *ESBL* extended spectrum beta-lactamases, *KPC Klebsiella pneumoniae* carbapenemase, *MBL* metallo-beta-lactamases, *NDM* New Delhi metallo-beta-lactamase [3, 5, 10]

found additional risk factors of international travel history (adjusted odds ratio aOR 2.0, $p = 0.008$), recent use of oral third-generation cephalosporins (aOR 2.3, $p = 0.021$) and being cared for at home (aOR 1.9, $p = 0.02$) [7]. The authors postulated that children in daycare may renew their microbiota with susceptible strains, thus explaining the higher risk for children cared for at home. A case-control study of children with ESBL infections in an American inpatient setting also

Table 2 Non-beta-lactamase mechanisms of antibiotic resistance in Gram-negative organisms

Antibiotic class	Mechanism of resistance	Organisms
Aminoglycosides	Target site mutation—production of 16S rRNA methylases	*E. coli* *K. pneumoniae* *P. aeruginosa* *Acinetobacter* spp.
	Drug modification—production of aminoglycoside-modifying enzymes Phosphotransferases (APH) Acetyltransferases (AAC) Nucleotidyltransferases (ANT)	*E. coli* *K. pneumoniae* *A. baumannii* *P. aeruginosa*
Quinolones	Target site mutation—DNA gyrase and topoisomerase IV	*E. coli* *Klebsiella* spp. *P. aeruginosa*
	Pentapeptide repeats—Qnr	*E. coli* *Klebsiella* spp.
Trimethoprim or trimethoprim-sulfamethoxazole	Overproduction of enzymes Dihydropteroate synthase (DHPS) Dihydrofolate reductase (DHFS)	*E. coli*

This table provides common/important examples rather than a comprehensive list [3, 5, 10]

reported international travel as a significant risk factor ($p < 0.001$) on multivariate analysis, as well as Asian ethnicity ($p = 0.003$) and gastrointestinal comorbidities ($p = 0.002$) [20]. Once children have been colonised with drug-resistant Enterobacterales, colonisation may persist for up to 4 years and perhaps longer [16].

Risks for colonisation with MDROs among hospitalised neonates include prolonged mechanical ventilation, prolonged hospital stay, use of invasive devices and antibiotic use [11]. Younger gestational age and low birth weight are risk factors for colonisation, but this may be due to longer hospital stay and more frequent antibiotic use [21]. There is also evidence of vertical transmission of ESBL-producing Enterobacterales, with colonisation rates of infants of ESBL-positive mothers being 6-fold higher when compared to infants of negative mothers in a neonatal intensive care unit [22]. A family-based study following detection of a multidrug-resistant ESBL-producing *E. coli* ST131-H30Rx strain causing febrile UTI in two siblings found that the offending strain was a prevalent and persistent coloniser in all six household members, supporting the hypothesis of transmission of intestinal colonisation among close contacts [23]. In this particular family, both parents had worked in the healthcare industry, prompting further consideration about the unknown rate of MDRO colonisation in healthcare workers and their families.

Risk factors for MDR UTI

There are a number of case-control studies regarding risk factors for UTIs with antibiotic-resistant organisms in children [6, 24–26]. The most frequently cited risk factors are previous antibiotic use, underlying urinary tract anomalies and previous hospitalisation. However, community-acquired 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. Up to 60% of infants with community-acquired ESBL-producing uropathogens in a recent retrospective Korean study had no identified risk factors [27]. A retrospective study in Taiwan showed no significant differences in risk factors between infants who did and did not have ESBL-producing organisms; 70% of the cohort had no risk factors [8]. This has implications for empiric prescribing in these settings.

Recent antibiotic use, including both therapy and prophylaxis, has been identified as a risk factor for MDR UTI, although timing of exposure differs between studies. An Australian case-control study showed that any antibiotic use within the last month, including antibiotic prophylaxis, was associated with an increased risk of MDR *E. coli* UTI [26]. An increased risk of UTI from an ESBL-producing organism was associated with use of antibiotics within the last 3 months in both Taiwan [24] and Turkey [25]. In a prospective study from the USA, there was a relative risk of 2.9 of having an ESBL-producing isolate following antibiotic use within the last 30 days, and 1.91 following antibiotic use within the last 90 days, when compared to those without antibiotic exposure [28]. Use of antibiotic prophylaxis for UTI has been associated with increased rates of ESBL-producing organisms [6]. A meta-analysis of six randomised controlled trials showed that patients receiving antibiotic prophylaxis for VUR were more likely to have MDRO for the first UTI (33% vs 6%, $p < 0.001$) and more likely to receive broad-spectrum antibiotics (69% vs 49%, $p = 0.004$) [29]. For every 21 patients with VUR treated with prophylaxis, one additional MDR recurrent UTI developed [29]. The prevalence of MDR UTIs varied widely depending on region, from 0 in Sweden to 62% in India.

Although use of antibiotics tends to increase the risk of drug resistance overall, no particular antibiotic has been demonstrated to increase the risk of UTI with an MDRO, and the evidence for antibiotic classes used for prophylaxis or treatment is mixed. In a Turkish study, although a history of previous use of third- or fourth-generation cephalosporins, fluoroquinolones, carbapenems or aminoglycosides was significantly higher in an ESBL-producing cohort, on multivariate analysis with logistic regression, no single antibiotic was identified as an independent risk factor [25]. In another study, one hospital in Taiwan found increased ESBL-producing *E. coli* with cephalosporin prophylaxis compared to co-trimoxazole prophylaxis, but this was not the case in the other hospital within the same study [30]. In a Turkish study, prior prophylaxis with co-trimoxazole or nitrofurantoin was higher in univariate analysis in a group with UTIs due to ESBLs, but this was not found to be a significant factor on multivariate analysis [25]. A retrospective study from Israel showed a correlation between recurrent UTI and development of resistance to second-generation cephalosporins, but not to aminoglycosides [31].

The presence of underlying genitourinary anomalies is associated with both recurrent UTIs and increased risk of MDRO. Urinary tract anomalies include VUR, hydronephrosis, dysplastic kidney, nephrolithaisis, bladder augmentation and Mitrofanoff procedures and other anatomical and functional anomalies [6, 12, 25]. One study found an increased risk of developing ESBL-producing (although not necessarily MDRO) UTIs with an underlying genitourinary anomaly with an OR of 4.8 [25]; another found the risk to be 2.7-fold [27]. One study found that recurrent UTI without underlying renal disease was not associated with an increased risk of ESBL-producing *E. coli* UTI [25]. A retrospective study of 3828 positive urine cultures in children that use clean intermittent catheterisation (CIC) found carbapenem-resistant Enterobacterales in 0.4% (70% *K. pneumoniae*, 20% *E. coli*, 10% *Enterobacter cloacae*), compared to 0.1% in a cohort of children who did not use CIC ($p < 0.001$) [32]. A further 4.5% of isolates in the CIC group were vancomycin-resistant *Enterococcus*. A randomised controlled trial showed no

benefit in using prophylactic antibiotics to prevent UTI in patients who used CIC, but that those with breakthrough UTIs were more likely to have resistant organisms [33].

Functional bladder bowel dysfunction (BBD) is a well-recognised risk factor for recurrent UTIs [34]. An analysis of the RIVUR study found that children with BBD were more likely to have urinary isolates that were resistant to at least one narrow spectrum antibiotic than children without BBD (OR 2.2, 95% CI 1.17 to 4.12) [35]. As yet, it is unknown whether BBD is an independent risk factor for UTIs due to MDRO.

Previous hospitalisation within the last 3 months was identified as a risk factor for UTIs with ESBL-producing organisms in two studies [6, 25], and within 1 month in two others [24, 36], particularly with admission to an intensive care unit within the last month [19]. There is also increased risk of development of UTIs with ESBL-producing organisms with non-genitourinary anomalies; malignancy, sepsis, diabetes mellitus, gastrointestinal anomalies, developmental delay and inherited disorders of metabolism, all have increased risk [12, 25]. It is unclear whether these are independent risk factors, or merely associated with recurrent and prolonged hospitalisation.

Global prevalence of MDRO colonisation and UTI in children

Most of the global data regarding surveillance of MDRO does not distinguish between adult and paediatric patients. Worldwide, approximately 1–5% of carbapenem-resistant Enterobacterales infections are in children [15]. The literature about MDRO UTI in children consists mainly of single-site epidemiological studies. There are several studies that focus purely on ESBL-producing *E. coli*, as summarised in Table 3. Studies that report MDROs are reported in Table 4.

Increasing incidence of drug-resistance has been reported in studies from several countries, with rates often doubling or more over 2 to 4 years. A British study found that 5.2% of isolates were ESBL producers, with an increased monthly incidence from 9.5 to 13.5 cases over a 2-year period [12]. Subtyping of *E. coli* strains in a Korean study showed significant increase in the O25b-ST131 clonal group, suggesting that clonal dissemination had contributed to a rapid increase in cases, as ST131 isolates were significantly more likely to be ESBL producers than non-ST131 *E. coli* strains [8].

Management

Treatment

Empiric treatment of suspected MDR UTI needs to be informed by local antibiotic susceptibility, with rationalisation of antibiotic therapy based on susceptibility results [1]. Some antibiotics used in adults are not approved for use in children [11], 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 (Fig. 1). Many community-acquired ESBL-producing Enterobacterales remain susceptible to oral agents such as fosfomycin and nitrofurantoin. Common intravenous options include carbapenems and aminoglycosides [36]; further options and their limitations are listed in Table 5.

Severe or complicated MDR UTI

In severe UTI with or without MDR, initial therapy should generally be intravenous. Examples of available agents are summarised in Table 5. For serious infection with ESBL producers, carbapenems are still commonly recommended as definitive therapy, particularly in cases of severe sepsis or life-threatening situations [1, 17, 37]. There are currently no studies comparing the different carbapenems in the treatment of MDR UTI in children. In adults with severe infections, a meta-analysis showed meropenem to have a greater bacteriological and clinical response than imipenem-cilastatin, with less adverse effects [38]. Ertapenem is another carbapenem used in the treatment of complicated infections which has the advantage of being a once daily dose which can be intramuscular, allowing for outpatient management once clinically stable [39].

Recently, there has been substantial interest in beta-lactam/beta-lactamase inhibitor (BLBLI) combination antibiotics as carbapenem-sparing agents. The MERINO trial investigated the treatment of adult patients with ceftriaxone-resistant *E. coli* or *K. pneumoniae* bloodstream infections, and found that piperacillin-tazobactam therapy did not result in a non-inferior 30-day mortality when compared to meropenem, suggesting that piperacillin-tazobactam should not be used in this setting [40]. UTIs were the source of bacteraemia in 54.8% and 67% of the piperacillin-tazobactam and meropenem cohorts, respectively [40]. Newer BLBLI such as meropenem-vaborbactam are used to treat carbapenem-resistant Enterobacterales and may represent future treatment options. The TANGO I trial found noninferiority of meropenem-vaborbactam, and indeed superiority, when compared to piperacillin-tazobactam in adults with pyelonephritis [41]. Meropenem-vaborbactam is not yet approved by the US Food and Drug Administration (FDA) for use in children. Ceftazidime-avibactam was shown to be non-inferior to doripenem in a Phase III trial of adults with complicated UTIs [42]. Unfortunately, neither has significant activity against MBL-producing organisms.

Aminoglycosides may also be useful to treat susceptible uropathogens, including many ESBL producers [1]; a comparative study in Israel on community-acquired ESBL showed that 50% of isolates showed resistance to

Table 3 Prevalence of ESBL-producing organisms causing UTI in children

Author Year Country	*N* Age range	Organisms	Proportion with ESBL as percentage
Ahmed et al. [35]	84	*E. coli*	48.8
2015	6 months–5 years	*K. pneumoniae*	
Tanzania		Other	
Degnan et al. [36]	370	Total Gram-negative	7.8
2015	0–18 years	*E. coli*	9.3
USA		*K. pneumoniae*	24.7
		K. oxytoca	35.3
Fan et al. [24]	312	*E. coli*	33.3
2014	0–15 years		
Taiwan			
Logan et al. [14]	363,398[a]	*E. coli*	0.5
2014	1–17 years	*K. pneumoniae*	
USA		*P. mirabilis*	
Parajuli et al. [37]	739	*E. coli*	38.9
2017	0–14 years		
Nepal			
Perez Haras et al. [34]	229	*E. coli*	9.2
2017	0–14 years		
Spain			
Rezai et al. [38]	327	*E. coli*	30.5
2015	Not stated		
Iran			
Sharma et al [39]	75	*E. coli*	48.0
2016	0–10 years		
India			
Topaloglu et al. [25]	4105	Gram-negative	3.8
2010	Not stated		
Turkey			
Yun et al. [40]	114	*E. coli*	14.0
2017	0–18 years		
South Korea			
Zerr et al. [28]	1204	Gram-negative	17.4
2016	0–21 years		
USA			

[a] Note only 62.11% of these from urinary sources

gentamicin but only 8% to amikacin [6]. Amikacin is active against most ESBL strains and may spare empiric carbapenem use, though caution must be taken to minimise aminoglycoside toxicity [1, 37]. A study in France demonstrated successful use of amikacin monotherapy for febrile UTI in children but only had two ESBL-producing isolates in their sample [37]. A small sample ($n = 28$) in Turkey showed successful use of amikacin monotherapy (7.5 mg/kg BD) for ESBL-producing *E. coli* UTI; the median time to resolution of fever was 2 days (range 1–3), and only one patient had treatment failure requiring switch to ertapenem [43].

Fluoroquinolones may be used in the treatment of complicated UTI [44], but use has been limited in children due to concerns about potential cartilage damage based on animal studies; more recent safety data shows that the most common adverse effects are gastrointestinal upset and some arthralgia, but no evidence of cartilage damage [44]. These agents generally have good bioavailability and can be given orally [5].

Polymyxin B and polymyxin E (colistin) may be used in MDR UTI; however, some guidelines recommend these be used in combination with another agent due to increasing development of resistance [10]. A recent retrospective study on the use of colistin in carbapenem-resistant Gram-negative

Table 4 Prevalence of MDR and XDR UTIs in children

Author Year Country	*N* Age range	Organisms	Proportion with MDR as percentage	Proportion with XDR as percentage
Raman et al. [26] 2018 Australia	2202 *E. coli* 1676 0–18 years	Gram-negative organisms *E. coli*	14.0 8.3	Not stated
Lagace-Wiens et al. [41] 2011 Canada	3789 total; subgroup 0–18 years (*N* not stated)	*E. coli*	11.6 in 0–18 year subgroup	Not stated
Sharma et al. [39] 2016 India	75 0–10 years	*E. coli*	90.0	Not stated
Yun et al. [40] 2017 South Korea	114 0–18 years	*E. coli*	26.3	Not stated
Parajuli et al. [37] 2017 Nepal	739 0–14 years	*E. coli*	64.0	5.0
Perez Haras et al. [34] 2017 Spain	229 0–14 years	*E. coli*	5.0	Not stated
Bryce et al. [42] 2018 UK	41 0–5 years	*E. coli*	17.1	Not stated

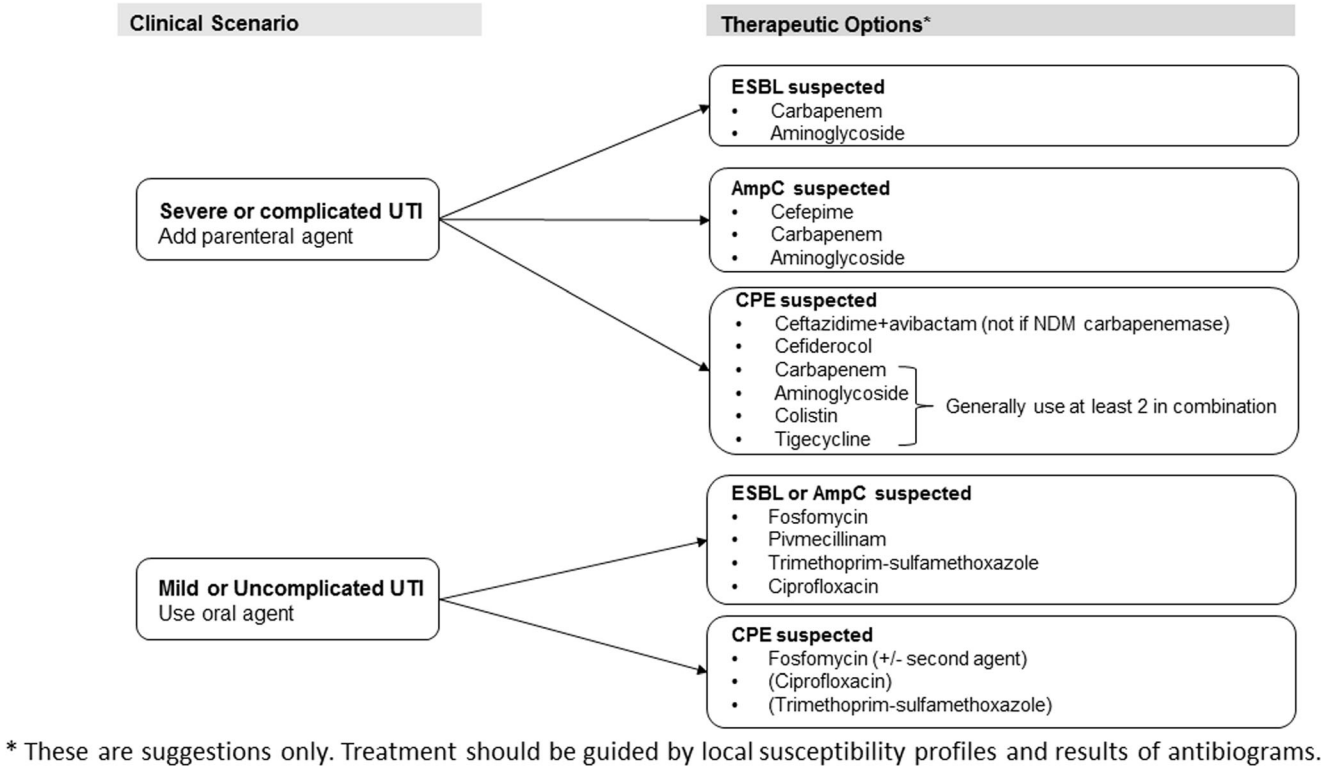

Fig. 1 Options for empiric treatment of urinary tract infection with high index of suspicion for MDRO. Readers should consult local guidelines, consider local epidemiology/antibiograms where available and modify therapy based on microbiology results and clinical progress, in consultation with infectious diseases/microbiology advice

Table 5 Parenteral antibiotics used for MDR UTI in children

Class	Agent	Adverse effects	Notes
Aminoglycoside	Gentamicin	Nephrotoxicity Ototoxicity	TDM recommended
	Amikacin	Nephrotoxicity Ototoxicity	TDM recommended
Beta-lactam + beta-lactamase inhibitor	Meropenem-vaborbactam	Headache	Not approved by FDA for use in children
Carbapenem	Ertapenem	Hepatic/gastrointestinal	
	Meropenem	Gastrointestinal	Prolonged infusion sometimes used in CPE as synergistic agent
Fluoroquinolone	Ciprofloxacin	Gastrointestinal Arthralgia	Only if no co-resistance present
Polymyxin	Colistin	Nephrotoxicity Neurotoxicity	
Synthetic tetracycline	Tigecycline	Dental staining/hypoplasia in < 8 years	Limited urinary penetration

TDM therapeutic drug monitoring, *FDA* United States of America Food and Drug Administration, *CPE* carbapenemase-producing enterobacteriacae [5, 10, 17, 44–47]

patients in a paediatric intensive care unit showed clinical response in 76% and microbiological response in 75.6%; three patients had UTI with central-line-associated bloodstream infection, one had UTI with ventilator-associated pneumonia and three patients had UTI alone [45]. And, 10.5% developed nephrotoxicity and none neurotoxicity [45].

A case series and review of all previous case reports of MDR or XDR Gram-negative bacterial infections in children found that tigecycline was reasonably well tolerated as a salvage therapy in serious infections, with mortality of 24% in non-bacteraemic infections and 80% in bacteraemic infections [46]. In this series, however, only one child had a UTI—a 7-year-old girl with underlying neuropathic bladder from herpes encephalitis and significant neurological deterioration had recurrent UTI with NDM-1-producing *E. coli* and *K. pneumoniae*. She was successfully treated with both tigecycline and fosfomycin [47]. Tigecycline can cause tooth discolouration and enamel hypoplasia, and there is limited paediatric data available, however, while it can be used as salvage therapy in combination with other agents; it should not be used as monotherapy for UTI in children as it has limited renal excretion [10].

Mild or uncomplicated MDR UTI

Oral agents potentially useful for cystitis or uncomplicated MDR UTI are summarised in Table 6.

Fosfomycin is bactericidal against a broad spectrum of aerobic bacteria and is generally given orally for treatment of UTIs [48, 49]. It has a unique mechanism of action, inhibiting cell wall synthesis of both Gram-positive and Gram-negative bacteria [50]. Uropathogens generally have low rates of fosfomycin resistance (< 2% in many countries, but up to 14.4% in South Korea and Spain) [48]. One possibility for this is that resistance to fosfomycin in Enterobacterales is chromosomally encoded, so though it may develop while on therapy, it is not transmitted by plasmids [49]. However, minimal paediatric data exist for this agent—a meta-analysis of fosfomycin as treatment for cystitis included only three paediatric studies from 1987 to 1990; only one of these involved patients with recurrent UTI [51]. Fosfomycin is reasonably well tolerated, with adverse effects occurring in 1–10% patients, most commonly gastrointestinal symptoms or infusion-related reactions associated with intravenous route [52]. There is variability in dosing recommendations, prompting the need for clinical trials to elucidate appropriate thresholds and dosing recommendations for children [52].

Pivmecillinam is recommended for empiric therapy of UTI in adults and children in many places in Northern Europe [51, 53]. In vitro studies suggest some effectiveness against ESBL-producing *E. coli*, particularly in combination with another agent such as amoxicillin-clavulanate [54]. However, the most recent studies on the use of pivmecillinam in children are for its use in shigellosis; the last randomised-controlled trial for its use in UTI in children was in 1991 [55, 56].

Nitrofurantoin is used for acute cystitis, and short-term use is generally well tolerated; susceptibility of ESBL-producing *E. coli* organisms to this agent is varied [51, 57]. Prolonged use is associated with polyneuropathy and interstitial fibrosis.

Amoxicillin-clavulanate may be used to treat cystitis and pyelonephritis in children over the age of 1 month, and is

Table 6 Oral antibiotics used in MDR UTI in children [17, 54–57]

Agent	Class	Examples of adverse effects	Notes
Fosfomycin	Unique	Gastrointestinal	
Nitrofurantoin	Synthetic nitrofuran analogue	Gastrointestinal Polyneuropathy Interstitial fibrosis with prolonged use	Limited renal tissue penetration so need high concentrations
Amoxicillin-clavulanate	Penicillin + beta-lactam inhibitor	Gastrointestinal Cholestatic hepatitis	
Pivmecillinam	Beta-lactam (synthetic penicillin)	Gastrointestinal	Not available in liquid formulation Achieves high urinary concentrations

generally well-tolerated [58]. It has been used both as a single agent in uncomplicated ESBL-UTI as well as part of combination therapy [54, 59].

Outcomes

MDRO UTI can lead to delayed initiation of appropriate therapy and poorer outcomes [4]. Community-acquired ESBL infections have more frequent early treatment failure [27], longer hospital stays, frequent complications and increased mortality; certain regions describe children having worse outcomes than adults with ESBL infections [11]. A case control study found that children with ESBL-*E. coli* UTI were more likely to need antibiotic adjustment following culture results, whereas children with non-ESBL UTI were more likely to be over-treated initially [24]. A recent study of paediatric infections with MDRO Enterobacterales found increased length of stay, ICU admissions and a trend towards a higher mortality rate; this study did not report the number of urinary infections in the sample [60].

Prevention

Infection control measures, such as hand hygiene, patient isolation, cohorting and having dedicated staff to care for patients may help to prevent the spread of MDRO [11]. Limiting overuse of antibiotics in agriculture and other non-human uses of antibiotics is also important for limiting resistance globally but beyond the scope of this review [11].

Antimicrobial stewardship programs have a critical role to play in reducing selection of resistant organisms through inappropriate or excessive antibiotic use [11]. An adult hospital reduced the incidence of ESBL-producing *K. pneumoniae* isolates by restricting third-generation cephalosporins via an electronic prescribing system [61].

The role of antibiotic prophylaxis for UTI in prevention of development of resistant organisms is controversial. Antibiotic prophylaxis has shown benefit in reducing febrile UTI in VUR; however, as described above, it can increase the prevalence of MDRO UTI through selection pressure. The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial showed that antibiotic prophylaxis halved the rate of febrile UTI, with an increase in subsequent trimethoprim-sulfamethoxazole-resistant *E. coli* UTI (63% compared with 16% with placebo) and a non-significant trend for increased resistant *E. coli* stool colonisation [62]. Overall, the benefits of reducing recurrent febrile UTI, and risking renal scarring and frequent hospitalisations, must be weighed against the risk of developing antimicrobial resistance.

Conclusion and recommendations

The management of MDRO in UTI in children remains challenging. Empiric prescribing guidelines must be tailored to local antibiograms and drug availability, in order to maximise clinical and microbiological cure while minimising unnecessary broad-spectrum antibiotic use. To date, there are no widely accepted guidelines on the management of MDRO UTI in children for this reason.

Further research into antimicrobial agents in children is essential. In particular, agents developed and used in adults to treat MDROs must be studied so they can be approved for use in children. Research into the pharmacokinetics and safety profiles of antimicrobials in children, and development of child-friendly formulations is essential to expand the treatment options for children worldwide. Antimicrobial stewardship and infection control programs are also crucial to reduce selection pressure for these resistant organisms.

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