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Review

Antibiotic Resistance in Paediatric Febrile Urinary Tract Infections

Susanna Esposito[1,*], Giacomo Biasucci[2], Andrea Pasini[3], Barbara Predieri[4], Gianluca Vergine[5], Antonella Crisafi[6], Cristina Malaventura[7], Luca Casadio[8], Marcello Sella[9], Luca Pierantoni[10], Claudia Gatti[11], Letizia Paglialonga[1], Chiara Sodini[1], Claudio La Scola[3], Luca Bernardi[1], Giovanni Autore[1], Giulia Dal Canto[1], Alberto Argentiero[1], Sante Cantatore[4], Martina Ceccoli[4], Alessandro De Fanti[6], Agnese Suppiej[7], Marcello Lanari[10], Nicola Principi[12], Andrea Pession[3], Lorenzo Iughetti[4]

[1] *Paediatric Clinic, University Hospital, Department of Medicine and Surgery, University of Parma, Parma, Italy*
[2] *Paediatrics and Neonatology Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy*
[3] *Paediatric Clinic, IRCCS Ospedale Maggiore Policlinico Sant'Orsola, Department of Medicine and Surgery, University of Bologna, Bologna, Italy*
[4] *Paediatrics Unit, Maternal-infantile Department, University Hospital, Department of Medicine and Surgery, University of Modena and Reggio Emilia, Modena, Italy*
[5] *Paediatrics Unit, AUSL Romagna, Rimini, Italy*
[6] *Paediatrics Unit, Santa Maria Nuova Hospital, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy*
[7] *Paediatric Clinic, University of Ferrara, Ferrara, Italy*
[8] *Paediatrics and Neonatology Unit, Ravenna Hospital, AUSL Romagna, Ravenna, Italy*
[9] *Pediatric Clinic, Azienda Sanitaria Locale Romagna, Cesena, Italy*
[10] *Paediatric Emergency Unit, IRCCS Ospedale Maggiore Policlinico Sant'Orsola, Department of Medicine and Surgery, University of Bologna, Bologna, Italy*
[11] *Paediatric Surgery, University of Parma, Parma, Italy*
[12] *Università degli Studi di Milano, Milan, Italy*

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ABSTRACT

Febrile urinary tract infection (UTI) is currently considered the most frequent cause of serious bacterial illness in children in the first 2 years of life. UTI in paediatrics can irreversibly damage the renal parenchyma and lead to chronic renal insufficiency and related problems. To avoid this risk, an early effective antibiotic treatment is essential. Moreover, prompt treatment is mandatory to improve the clinical condition of the patient, prevent bacteraemia, and avoid the risk of bacterial localization in other body sites. However, antibiotic resistance for UTI-related bacterial pathogens continuously increases, making recommendations rapidly outdated and the definition of the best empiric antibiotic therapy more difficult. Variation in pathogen susceptibility to antibiotics is essential for the choice of an effective therapy. Moreover, proper identification of cases at increased risk of difficult-to-treat UTIs can reduce the risk of ineffective therapy. In this review, the problem of emerging antibiotic resistance among pathogens associated with the development of paediatric febrile UTIs and the best potential solutions to ensure the most effective therapy are discussed. Literature analysis showed that the emergence of antibiotic resistance is an unavoidable phenomenon closely correlated with the use of antibiotics themselves. To limit the emergence of resistance, every effort to reduce and rationalise antibiotic consumption must be made. An increased use of antibiotic stewardship can be greatly effective in this regard.

Background

In the last 20 years, the large-scale use of conjugate vaccines against *Haemophilus influenzae* and *Streptococcus pneumoniae* has dramatically reduced the number of severe bacterial infections of infants and young children, including bacteraemia and meningi-

* Address correspondence to: Susanna Esposito, Pietro Barilla Children's Hospital, Department of Medicine and Surgery, University of Parma, Via Gramsci 14, 43126 Parma, Italy, Phone: +39 0521 903524.
E-mail address: susanna.esposito@unimi.it (S. Esposito).

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Table 1
Standard empiric treatment for paediatric febrile urinary tract infections according to clinical presentation [11-16].

* The use of quinolones should be limited to patients whose clinical condition is severe or who are unresponsive to other antibiotics, only on the basis of sensitivity patterns.
** Because of the increasing rate of resistance, according to most guidelines, the empirical use of trimethoprim should be avoided.

tis [1,2]. This has made more evident the clinical relevance of febrile urinary tract infection (UTI), which is currently considered the most frequent cause of serious bacterial illness in children in the first 2 years of life [3]. Febrile UTI, generally considered indicative of upper UTI named pyelonephritis, can irreversibly damage the renal parenchyma and lead to chronic renal insufficiency and related problems. To avoid this risk, it is essential that antibiotic treatment effective against the causative bacterial pathogen be administered within 3-4 days of fever onset [4-7]. On the other hand, prompt treatment is essential to improve the clinical condition of the patient, prevent bacteraemia, and avoid the risk of bacterial localization in other body sites [8].

Unfortunately, definitive diagnosis of UTI and identification of the infecting pathogen are frequently delayed, and initially administered therapy remains empiric (Table 1). In infants and young children, signs and symptoms of disease are nonspecific. Fever without a source is commonly the only initial manifestation of a renal infection, which can hinder a prompt diagnosis [9]. Moreover, to avoid invasive methods, collection of urine for culture, the only method to diagnose UTI, is generally performed with a sterile bag applied to the perineum or clean catch midstream void. However, with these methods, false positive results, which require confirmation with a second invasive test and delay the choice of the most effective antibiotic therapy, are common [10]. This drawback explains why it is recommended that when on the basis of clinical manifestations and/or laboratory tests, pyelonephritis is strongly suspected, empiric antibiotic treatment must be initiated soon after a urine specimen for culture has been obtained, even if diagnosis is not definitive and the infecting pathogen and its sensitivity to antibiotics are not precisely defined [11-15].

To assure the highest probability of bacterial eradication, official guidelines indicate which antibiotics must be used. The list is periodically updated considering the variations over time in the sensitivity of uropathogens to antibiotics [11-16]. However, despite the difference between inpatients and outpatients [17], antibiotic resistance for UTI-related bacterial pathogens continuously increases, making recommendations rapidly outdated and the definition of the best empiric antibiotic therapy more difficult. This means that, at least in some cases, recommended empiric treatment can fail, with a potential increased risk of immediate or long-term complications [18-22]. Awareness of upper UTI aetiology and variation in pathogen susceptibility to antibiotics is essential for the choice of an effective therapy. Moreover, proper identification of cases at increased risk of difficult-to-treat UTIs can reduce the risk of ineffective therapy. In this review, the problem of emerging antibiotic resistance among pathogens associated with the development of paediatric febrile UTIs and the best potential solutions to ensure the most effective therapy will be discussed. A literature search was performed in Medline, Embase and the Cochrane Library. The terms children and urinary tract infections or derivatives hereof were used. A total of 1,440 English language abstracts were screened for their relevance and 101 full texts were obtained for appraisal. Publications were included when the results described aetiology or uropathogens resistance or antibiotic therapy for children with UTI or when the publication introduced new evidence about antibiotic resistance in paediatric UTIs.

Aetiology of urinary tract infections (UTI)

Febrile UTI is due to bacteria in almost all cases without any relevant difference according to gender. Viruses, such as adenoviruses, enteroviruses, echoviruses and coxsackieviruses, can rarely cause UTI, but the infection is usually limited to the lower urinary tract [23]. Fungi, mainly *Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans*, can be associated with pyelonephritis, but this type of infection occurs very rarely and generally in children with select clinical conditions, such as long-term antibiotic therapy, history of urinary tract medical implants or severe immune deficiency [24].

Gram-negative rods coming from the intestinal microbiota are the main pathogens of UTI. *Escherichia coli* is the most common in all ages, both in hospital and community contexts, accounting for up to 90% of all the causative agents [9,25,26]. This is because *E. coli* possesses several types of adhesins that facilitate adherence of the pathogen to the uroepithelium despite the flushing effect of urine flow [27]. Moreover, once the urinary tract is invaded, an intracellular biofilm that protects the pathogen from the host immune system is produced [28]. Other common gram-negative uropathogens are *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Proteus mirabilis*. Their relevance, relatively poor in first up-

per UTIs in otherwise healthy children, increases significantly in recurrent cases already treated with several antibiotic courses and in those secondary to invasive procedures or indwelling catheters [29-31]. Curiously, several studies have demonstrated that although *E. coli* is the most frequent causative organism at all ages independent of patient demographic characteristics, it is more often found in females, while *K. pneumoniae* and *P. mirabilis* are more common in males [32,33]. Gram-positive bacteria, such as *Staphylococcus aureus, viridans* group streptococci, and *Streptococcus pneumoniae*, rarely cause upper UTIs, as they are cultured in no more than 5% of cases. They generally cause lower UTIs, and cases of upper urinary tract involvement are limited to a small number of children with urinary flow alterations due to anatomical, functional or neurological causes and in patients with compromised immune systems [34,35]. *Staphylococcus saprophyticus*, which is the agent of up to 15% of lower UTIs in adolescents and sexually active girls, is rarely found in pyelonephritis [36]. Finally, in neonates, where Gram-negative rods remain prevalent, group B *Streptococcus* infections can occur [37].

Mechanism of uropathogen resistance

Several mechanisms of uropathogen resistance to antibiotics have been described. The most widespread is the production of extended spectrum beta-lactamases (ESBLs), i.e., enzymes that hydrolyse beta-lactam antibiotics [38]. Bacteria carrying ESBLs, mainly *E. coli, K. pneumoniae* and *P. mirabilis*, are resistant to penicillins, first- to third-generation cephalosporins, and aztreonam, although they remain generally susceptible to cephamycins (cefoxitin) or carbapenems. Moreover, as ESBLs are generally inactivated by substances that act as suicide substrates (clavulanate, tazobactam and sulbactam), bacteria carrying ESBLs are sensitive to the combination of a beta-lactam with one of these inhibitors. The combinations ampicillin/clavulanate and ampicillin/sulbactam are the most widely used among the oral and parenteral preparations, respectively. As most of the genes that encode ESBL production are carried in plasmids, ESBL-mediated resistance is easily transmissible, which explains why this kind of bacterial resistance has spread worldwide in a relatively short time [38].

A number of bacteria can produce beta-lactamases different from ESBLs. AmpC cephalosporinases can be chromosomally encoded or carried by plasmids [39]. They act similarly to ESBLs but also make pathogens insensitive to combination drugs, as they are not inhibited by clavulanic acid and similar inhibitors. However, carbapenems, fourth-generation cephalosporins, and avibactam remain active. Together with *E. coli* and *K. pneumoniae, Citrobacter freudii, Serratia marcescens, Morganella morganii,* and *Providencia stuartii* are among the most common UTI pathogens with AmpC cephalosporinases [39].

Carbapenemases recognize almost all hydrolysable beta-lactams, including carbapenems, and most are resistant to all beta-lactamase inhibitors [40]. However, as different carbapenemases with various hydrolytic activities have been identified, susceptibility to carbapenem antibiotics of a given pathogen can vary according to the type of enzyme produced by this agent. Carbapenemases are categorized in Ambler classification system as follows: the class A carbapenemases (GES, KPCs) which are inhibited by clavulanic acid; the class B or metallo-β-lactamases (VIM, IMP, NDMs) which are inhibited by ethylene diamine tetra-acetic acid (EDTA); and the class D oxacillinases which are not affected by clavulanic acid or EDTA [41]. Widespread use of carbapenems resulted in the emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) also in paediatric age [42]. *E. coli, K. pneumoniae, K. oxytoca, S. marcescens, Enterobacter* spp. and *C. freudii* can carry carbapenemases. *In vitro* aminoglycosides, glycopeptides, fosfomycin, polymyxins (colistin), tigecycline, plazomicin and new members of the tetracyclines, such as eravacycline, are generally effective against these strains [40]. The polymyxins (colistin and polymyxin B) are considered antibiotics for treating such infections [43]. However, pharmacokinetic and pharmacodynamic data on the use of polymyxins in children are very limited, and there are safety concerns. Polymyxin B appeared to be a better therapeutic option, with more rapid and higher steady state concentrations achieved compared to colistin and less reported nephrotoxicity [43]. Interestingly, in adults the combination of aztreonam (ATM) with ceftazidime-avibactam (CAZ-AVI) showed therapeutic advantages in patients with bloodstream infections due to metallo-β-lactamase–producing *Enterobacterales* treated either with CAZ-AVI plus ATM or other active antibiotics [44]. There is virtually no data in children currently. There is therefore an urgent need for pharmacokinetic and safety trials in these populations to determine the optimal drug and dosing regimens and provide recommendations for their use against carbapenem resistant infections [45-47].

A nonmarginal number of uropathogens simultaneously exhibit several mechanisms of resistance to antibiotics. When a pathogen is resistant to one or more antibiotics in three or more different antibiotic classes, it is defined as multidrug resistant (MDR), whereas nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories defines extensively drug resistant (XDR) pathogens [48]. Among MDR and XDR pathogens, *E. coli, K. pneumoniae, P. aeruginosa*, and *Acinetobacter* spp. are the most common. In these cases, pathogens are insensitive to beta-lactams due to the presence of ESBLs or other beta-lactamases and to aminoglycosides, fluoroquinolones, sulphonamides and colistin. Alterations in the ribosomal binding of the drug, reduced permeability and enzyme inactivation are responsible for aminoglycoside resistance [49]. Quinolone resistance is mediated by mutations that alter the drug target, i.e., the bacterial enzymes DNA gyrase and DNA topoisomerase IV, mutations that modify influx and efflux of the drug, and plasmids that produce a protein that protects the quinolone targets from inhibition [50]. Trimethoprim and sulphonamide resistance depends on the presence of alternative drug-resistance variants of the drug target, i.e., the enzyme dihydropteroate synthase in the folic acid pathway [51]. Colistin resistance is mediated by *mcr* genes and represents an emerging public health threat worldwide, including but not limited to humans, environment, waste water treatment plants, wild, pets, and food producing animals [52]. Cefiderocol and meropenem/vaborbactam should be considered potential options to treat MDR *P. aeruginosa* and *A. baumanii* and KPC-producing CRE, respectively [53,54]. Table 2 summarises available antibiotic treatments according to causative pathogens and resistance pattern.

Incidence of resistant uropathogens

In recent years, the incidence of uropathogen resistance to commonly used antibiotics for paediatric UTI has increased worldwide. In the USA, out of 368,398 isolates in children with UTIs between January 1999 and December 2011, 1.97% were identified as third-generation cephalosporin resistant, and 0.47% were identified as ESBL producers [55]. The prevalence of both phenotypes increased from 1.39% and 0.28% in 1999-2001 to 3% and 0.92% in 2010-2011, respectively. The increase was significant in all demographic and age groups, including outpatients, with the highest proportion of isolates in children aged 1-5 years. An increase in the detection of resistant uropathogens was also reported in a British study showing that the monthly incidence of ESBL UTI among children was 9.5% (95% confidence interval [CI] 7–15.5%) in 2014 and 13.5% (95% CI 12–17.5%) in 2015, although the difference was not statistically significant [56]. In Turkey, comparing the data collected in a single paediatric institution from 2009 to 2014, it was shown that *E. coli*

Table 2
Available antibiotic treatments according to causative pathogens and resistance pattern.

Pathogens	Treatments
Enterobacteriaceae	Ampicillin-Sulbactam or Amoxicillin-Clavulanic acid Third-generation cephalosporins Aminoglycosides
ESBL-producing *Enterobacteriaceae*	Ampicillin-Sulbactam or Amoxicillin-Clavulanic acid or Piperacillin/Tazobactam Aminoglycosides Urosepsis → Carbapenems
Carbapenemase-producing *Enterobacteriaceae*	Polymyxins (colistin and polymyxin B) Aztreonam + ceftazidime-avibactam
Pseudomonas aeruginosa	Ceftazidime Piperacillin-Tazobactam Carbapenems Resistant strains → beta-lactam + aminoglycoside or beta-lactam + ciprofloxacin or Ceftazidime-Avibactam
Enterococcus spp.	Ampicillin-Sulbactam + Gentamicin Penicillin resistance → Vancomycin + Gentamicin Aminoglycoside resistance → Ampicillin-Sulbactam + Ceftriaxone Vancomycin resistance → Linezolid or Tigecycline
Cephalosporinase-producing pathogens	Fourth-generation cephalosporins Aminoglycosides Carbapenems
MDR pathogens	Carbapenems Cefiderocol Carbapenemase-producing strains → Ceftazidime-Avibactam or Polymyxin + Carbapenem or Polymyxin + Tigecycline or Meropenem/vaborbactam

ESBL, extended spectrum beta-lactamases; MDR, multidrug resistant.

resistance during the study period increased for ampicillin from 47.1% to 89%, for trimethoprim-sulphamethoxazole from 44.8% to 56% and for nitrofurantoin from 5.3% to 15.1% [57].

Several factors can explain the development of antibiotic resistance and its progressive increase, mainly the inappropriate use of these drugs. Antibiotics are among the drugs most commonly prescribed to children in hospital and community settings [58,59]. Unfortunately, a great number of these antibiotic prescriptions are unnecessary or inappropriate, as shown by the evidence that these drugs are frequently given to children who do not suffer from bacterial diseases or do not have an infectious disease. In other cases, broad-spectrum antibiotics are given to children who suffer from infections for which narrow-spectrum drugs are indicated and recommended. Finally, many children receive antibiotic prescriptions indicating an incorrect total daily dosage or fractioning or for a period of time significantly longer than needed [60]. Regarding UTIs, one of the most common causes of microbial selection and emergence of resistance is the administration of antibiotics for prophylaxis in children with recurrent UTI episodes, especially when a structural or functional abnormality of the urinary tract has been diagnosed. In most cases, prophylaxis has not been proven beneficial for preventing new renal scarring in children and is no longer recommended in official guidelines. Despite this lack of recommendation, it is maintained in many children, favouring the emergence of resistance and the development of difficult-to-treat new UTI episodes [61]. The implementation of strategies to preserve the activity of existing antimicrobial agents has become an urgent public health priority for paediatric infections. Antimicrobial stewardship (AS) is one such approach [60]. Development of local AS teams including experts from different fields is considered essential to ensure adequate development of AS programs and continuously updated information useful for avoiding antibiotic misuse and abuse [62]. Infectious disease, pharmacy, microbiology, infection control, and information technology specialists need to be involved and offer support and continuous medical education to paediatricians regarding the prescription of antibiotics. AS strategies have had a significant impact on reducing targeted- and nontargeted-antimicrobial use, improving quality of care of hospitalized patients and preventing the emergence of resistance [60,62]. Only by making AS daily practice, through the use of financial resources and dedicated staff, it is possible to fight antimicrobial resistance, ensuring safe and effective care for young patients.

Generally, recent studies in children with UTI have shown that *E. coli* was the pathogen with the highest incidence of antibiotic resistance and that the production of ESBLs was the most common cause of this emerging phenomenon, although with differences among countries and within the same country. In Nepal, among 738 *Escherichia coli* isolates, 38.9% were ESBL producers, a value quite similar to that found in other developing Asian countries, such as India [63], Iran [64], and Cambodia [65], where the prevalence of *E. coli* ESBL producers was 37%, 44%, and 41.4%, respectively. Lower values were reported in South Korea (10.2%) [66], Taiwan (14.1%) [67], and Lebanon (20.2%) [68]. In Turkey, after a first report of a study carried out in Ankara revealed a prevalence of 64.5% [69], a second study collecting UTI cases diagnosed in Istanbul showed a prevalence of 41% [70]. In the USA, studies carried out in different institutions revealed the presence of ESBL-*E. coli* in 9.3% [71] and in 16.8% [72] of cases.

K. pneumoniae is the second most common organism associated with ESBL production, and in several studies, the incidence of ESBL production by this pathogen was found to be significantly higher than that of ESBL *E. coli* producers. For example, in the study by Degnan et al. [71], in which 9.3% of *E. coli* were ESBL producers, 24.7% of cultured strains *of K. pneumoniae* were ESBL producers.

In many studies, a significant proportion of uropathogens were MDR or XDR organisms. In a study carried out in Australia involving 2202 UTIs due to gram-negative organisms, 308 (14.0%) were caused by MDR strains. All the tested bacteria were resistant to ampicillin, more than 80% were resistant to trimethoprim, and approximately 50% were resistant to gentamicin, cephalexin and ceftriaxone. The combination of amoxicillin/clavulanic acid remained effective in more than 20% of the cases [73]. In Nepal [74], among 739 *E. coli* isolates, 480 (64.9%) were MDR and 37 (5.0%) were XDR. MDR strains were resistant to ampicillin, amoxicillin/clavulanate, cephalexin and ciprofloxacin in 100%, 84.7%, 81.6%, and 80.6%

of the cases, respectively. However, MDR *Escherichia coli* isolates remained susceptible to amikacin (87%), imipenem (92%) and piperacillin/tazobactam (81%). XDR isolates were totally resistant to all antibiotics except colistin and tigecycline, which were effective against all the tested pathogens. In a retrospective 8-year study in children hospitalised for UTI in the Emilia-Romagna Region, Italy, we showed that 840/1801 cases (46.7%) were due to antimicrobial-resistant uropathogens: 83 (4.7%) to ESBL, 119 (6.7%) to MDR and 4 (0.2%) to XDR bacteria [75]. The most frequent ESBL pathogens were *E. coli* (62/83, 74.7%) and *K. pneumoniae* (10/83, 12.0%), and the most frequent MDR pathogens were *E. coli* (68/119, 57.1%), *P. aeruginosa* (12/119, 10.1%), *K. pneumoniae* (7/119, 5.9%) and *Proteus mirabilis* (6/119, 5.0%). XDR pathogens were *E. coli* (3/4) and *K. pneumoniae* (1/4). Having ESBL or MDR/XDR uropathogens was significantly associated with treatment failure [75].

Risk factors for the development of febrile urinary tract infection (UTI) due to resistant bacteria

Considering the potential clinical importance of febrile UTI due to resistant pathogens, several studies have tried to evaluate which factors could favour the development of such infections. In some of these studies, the importance of some sociodemographic features, such as age and ethnicity, has been highlighted. Although antibiotic resistance is usually more frequent among hospital-acquired than community-acquired infections [42,62], available data in paediatric UTIs are mainly related to community-acquired infections. The logistic regression analysis of the results of a study enrolling 344 children revealed that age <1 year was associated with a 1.74-fold increase in the risk of the presence of ESBL-producing bacteria [70]. Moreover, in Israel, it was evidenced that the rate of ESBL-UTI was significantly higher in Arab children than in Jewish children (odds ratio [OR] 6.1; 95% CI 2.7–13.6) [76]. However, despite differences among studies [77], the most reported predisposing factors for the development of resistant febrile UTI were the presence of urinary system structural or functional abnormalities, including vesicoureteral reflux (VUR), recurrent UTI, and administration of continuous antibiotic prophylaxis, particularly when based on cephalosporins [68-70,76,78]. Compared to that in children without VUR, the OR for the development of UTIs caused by ESBL-*Enterobacteriaceae* in children with VUR was 2.79 (95% CI 1.39-5.58; p=0.004). Similarly, in children with recurrent UTI, the OR was 2.89 (95% CI 1.78-4.68; p<0.001) [79]. Finally, prophylaxis with cephalexin was found to be significantly more frequent (32%) in children with resistant UTIs than in those with UTIs associated with sensitive pathogens (2%; p<0.005) [80].

However, a more in-depth analysis of available data seems to indicate that even in children without urinary tract abnormalities, UTI recurrences and long-term prophylaxis can develop in febrile UTIs due to resistant pathogens. Pooling the results of 3 studies [29,68,76], Flokas et al. [79] showed that antibiotic therapy within 30 days before infection was the only independent risk factor for the development of a resistant UTI (OR 3.92, 95% CI 1.76-8.7). The strict relationship between previous antibiotic use and the development of resistant UTI was confirmed by several other studies carried out in children seen both in the hospital and in primary care settings. Among hospitalised children with UTIs, Raman et al. [73] compared the characteristics of 86 cases with MDR gram-negative rods with those of the same number of children without and found that the only significant risk factor for difficult-to-treat UTIs was antibiotic use in the previous month (adjusted OR 3.0, 95% CI 1.4 - 6.2). A systematic review and meta-analysis of 58 observational studies investigating 77,783 *E. coli* isolates from children with UTI revealed that children who had received previous prescriptions for antibiotics in primary care settings were more likely to have an infection due to resistant strains and that this increased risk could persist for up to six months (OR 13.23, 95% CI 7.84-22.31) [81].

Finally, a number of studies suggest that resistant UTI can occur even in children without any of the previously reported risk factors. A study carried out in Korea has shown that up to 60% of infants with UTI due to community-acquired ESBL-producing pathogens had no identified risk factors capable of explaining the phenomenon [18]. Similar findings were reported in a retrospective study in Taiwan that did not find significant differences in risk factors between infants who did and did not have ESBL-producing organisms, with 70% of the cases who had no risk factors in both groups [82]. Although rectal swabs positive for MDR bacteria are considered risk factors for invasive infections in neonatal intensive care units [83], there are no data about the role of rectal colonization by MDR pathogens in increasing the risk of UTI caused by resistant pathogens in paediatric age.

Clinical relevance of resistance

For many years, it has been known that untreated pyelonephritis in children can lead to irreversible renal damage and the development of uraemia and hypertension in adults [84,85]. Consequently, prompt diagnosis and proper management of acute febrile UTI in children has always been considered mandatory. However, with the increase in antibiotic resistance of uropathogens, the definition of the most appropriate antibiotic treatment is challenging, although all the official recommendations indicate that antibiotics must be administered by mouth unless the UTI is diagnosed in children who appear septic or severely dehydrated or are vomiting or if concerns regarding compliance are present. This is because several studies have stated that there was no difference in efficacy between oral and parenteral treatment [86,87].

In children with previous episodes of UTI and/or well-defined structural or functional abnormalities of the urinary tract, the risk of resistance is high, and the choice of antibiotic therapy must take into consideration the aetiology of previous episodes and local antimicrobial resistance data. If these are not available, it must be considered that most resistant pathogens are ESBL producers and that first- to third-generation cephalosporins are ineffective. The amoxicillin/clavulanic acid combination seems to be the best solution, although all these patients must be carefully monitored, and culture results can lead to substantial modifications if the infecting pathogens are not sensitive to the combination. When AmpC cephalosporinase producers are detected, carbapenems and aminoglycosides are indicated. Although there are currently no studies comparing the different carbapenems in the treatment of MDR UTIs in children, ertapenem could be used, as this drug has the advantage of being administered only once per day and has been found to be effective in the treatment of paediatric complicated UTIs due to ESBL-producing bacteria in children [88]. On the other hand, in adults, it was found to be seemingly more effective than meropenem, which, in turn, was more efficacious than imipenem-cilastatin [89]. Aminoglycosides are generally effective against ESBL producers: a study carried out in 28 children with these pathogens receiving amikacin showed that the drug was effective in all but one for whom a switch to a carbapenem was required. Amikacin should be preferred to gentamycin, as a study carried out in Israel reported that among ESBL producers, 50% of isolates were resistant to gentamycin and only 8% to amikacin [80]. Eradication of carbapenemase-producing bacteria can be very difficult. Data collected in children with UTIs are scant, and no treatment is considered of choice. In adults, tigecycline and a series of combinations, such as colistin (polymyxin E) and carbapenem; colistin and tigecycline; colistin and fosfomycin; and double carbapenem therapy,

have been found to be effective [90]. Combinations of these agents can be used in MDR or XDR UTIs.

In first febrile UTI episodes, the risk of resistant strains is lower. However, the evidence that resistance can also be demonstrated in children without risk factors and in those who have received a recent antibiotic therapy even if unrelated to a previous UTI suggests that a certain number of children with the first febrile UTI could receive an ineffective drug if treated with conventional therapy. The consequences of ineffective antibiotic administration are not precisely defined [91], although the presence of resistant uropathogens has been associated with poor outcome and risk of complications. Meropol et al. [19] reported that MDR *Enterobacteriaceae* infections could lead to a 19.8% increased mean length of stay (95% CI 9.9–30.5%; $p<0.001$) and a trend towards a higher mortality rate (OR 1.54, 95% CI 0.99–2.4; $p=0.058$).

However, the risk of ineffective therapy is strictly related to the local incidence of resistant bacteria and the updating of the recommendations of official guidelines. Taking into account the increase in the incidence of ESBL cases, Italian guidelines have recently been updated, and an amoxicillin/clavulanic acid combination has been indicated as the drug of choice for paediatric UTI treatment, highlighting that first- to third-generation cephalosporins have no additional role in this regard, as they are, in many cases, ineffective against ESBL-producing strains [12]. In contrast, although updated in 2016 [92], the American Academic of Pediatrics guidelines did not change previous recommendations that included some first-generation cephalosporins (cefixime, cefpodoxime, cefprozil, cefuroxime axetil, and cephalexin) as potentially effective drugs for the treatment of paediatric first UTI [13]. Similar limitations seem to be present in the NICE guidelines that, despite being updated in 2018, still indicate cefalexin as a first-line drug and recommend the use of amoxicillin/clavulanic acid only when culture results are available and the pathogen is found sensitive to the combination [14].

Fortunately, practice shows that the risk of serious immediate or long-term clinical problems from the use of discordant therapy is lower than expected. Although with exceptions, studies that have evaluated the outcome of febrile paediatric UTIs according to the administered antibiotic therapy have shown that in a relevant number of cases, the outcome of children receiving drugs that are ineffective against the infectious pathogen *in vitro* did not differ from that of those given a concordant therapy. Most of the data in this regard have been collected in children with ESBL-producing *Enterobacteriaceae*. Katsuta et al. reported that 72% of children with pyelonephritis caused by these pathogens became afebrile in $\leq$2 days and had an excellent clinical outcome despite being treated with antimicrobials ineffective against these organisms [93]. Clinical and microbiologic outcomes as well as the formation of renal scars did not differ between patients with and without ESBL-producing strains, although in the former, only 14% had received appropriate empiric therapy [94]. Madhi et al. found that the time to apyrexia and length of hospital stay did not differ in patients with or without effective empirical therapy against ESBL-producing *Enterobacteriaceae* [95]. Finally, a very recent multisite retrospective study regarding 230 children with UTI due to ESBL-producing *E. coli* or *K. pneumoniae* who had been treated with a third-generation cephalosporin showed that, despite discordant antibiotics, 192 (83.5%, 95% CI 78.0–88.0%) had overall clinical improvement. In only 7 patients (3.0%, 95% CI 1.2–6.1%), escalation of care, defined as an emergency department visit or hospitalisation for outpatients or transfer to the intensive care unit for patients already hospitalised, was needed [96].

At least two factors might explain why febrile UTIs can be cured even in the absence of effective *in vitro* antibiotic therapy. A certain number of febrile UTIs can resolve spontaneously, as has been demonstrated for other bacterial diseases, such as streptococcal pharyngitis [97] or acute otitis media [98]. Data collected by Newman et al. [99], studying the predictors and results of urine testing of young febrile infants, strongly support this hypothesis. These authors reported that 807 infants were not initially tested or treated with antibiotics, and approximately 61 should have had a UTI based on their sex, circumcision status, temperature, and other predictors of UTI. However, that diagnosis was subsequently made only in 2 cases, suggesting that in most infants, at least the acute symptoms of UTI subsided spontaneously. Second, it cannot be excluded that the administered antibiotic can reach urine and renal parenchyma concentrations much higher than those achieved in blood after usual doses and that are used to define resistance in vitro. Several antibiotics have peculiar pharmacokinetic properties and are concentrated in some organs and body fluids, reaching levels significantly higher than those defining resistance, achieving pathogen eradication despite the pathogen being considered resistant *in vitro* [100]. Concentrations of all beta-lactams and beta-lactamase inhibitors are significantly higher in urine than in serum [100]. All aminoglycosides are concentrated in the renal parenchyma [101]. In both cases, it seems likely that, at least in some cases, eradication of the pathogens at the site of infection can occur despite discordant therapy.

Conclusions

Febrile UTIs of infants and children, despite being very common and largely studied, remain a challenging problem. Regarding therapy, the increase in resistance of uropathogens to commonly used antibiotics requires continuous monitoring of microbiological characteristics of UTIs along with updating recommendations for antibiotic choice. The emergence of antibiotic resistance is an unavoidable phenomenon closely correlated with the use of antibiotics themselves. However, to limit the emergence of resistance, every effort to reduce and rationalise antibiotic consumption must be made. An increased use of AS can be greatly effective in this regard.

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Competing interests

All the authors have no competing interest to declare.

Ethical approval

Not required.

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