Treatment of Urinary Tract Infections Caused by ESBL-producing Escherichia coli or Klebsiella pneumoniae

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Urinary tract infections (UTIs) are usually caused by Gram-negative Enterobacteriaceae, the most common pathogens being Escherichia coli and Klebsiella pneumoniae. Antimicrobial resistance is increasing among uropathogens and the production of β-lactamases is a major resistance mechanism. Extended spectrum β-lactamases (ESBLs) producing pathogens exhibit resistance not only to newer β-lactams, including third generation cephalosporins and monobactams, but also to other classes of antibiotics. ESBL resistance genes are located on plasmids which are transferrable to other strains, thus posing considerable infection control issues. UTIs caused by ESBL-producing E. coli and K. pneumoniae are the most common ESBL infections in childhood. Herein, we summarize available data on these pathogens with a focus on treatment choices.

BETA-LACTAMASES AND ESBL CLASSIFICATION

Beta-lactamases are classified either by their structure or by their functional properties. The structural way was based on protein sequence and active site of the enzymes and classified β-lactamases into 4 classes, A, C and D serine β-lactamases and B metallo-β-lactamases. A functional classification correlated the properties of a specific enzyme with the resistance profile of a clinical isolate and included 3 major groups, 1, 2 and 3 with subgroups. In Table 1, we summarize the clinically important β-lactamases produced by resistant E. coli and K. pneumoniae uropathogens.

EPIDEMIOLOGY OF ESBL E. COLI AND K. PNEUMONIAE UROPATHOGENS

The first transferrable β-lactamase was named TEM, after the name of a patient in Greece in the early 1960s with an E. coli–positive blood culture. The first ESBL enzyme of sulphydryl variable type was identified in a Klebsiella strain isolated in Germany in 1983. Until 2000, ESBL-producing Enterobacteriaceae caused mainly nosocomial infections. However, with the gradual predominance of cefotaximase of Munich (CTX-M) producing strains and after introduction of E. coli ST131 (a CTX-M-15 strain), they quickly spread to the community. Despite the international surveillance programs, data on ESBL uropathogens in children remain limited. In a meta-analysis, an ESBL prevalence of 14% was found among 7374 urine isolates, with E. coli and Klebsiella spp. being the most common. Rates were high in Africa (76%) and South-East Asia (37%), intermediate in Europe (12%) and Eastern Mediterranean (5%) and lowest (2%) in the Americas. ESBL rate was 5% among community-acquired UTIs and 12% among healthcare-associated ones.

Global trends for AmpC uropathogens are not available but surveillance programs suggest high rates in regions with high ESBL prevalence. In a multicenter study from China, 2% of E. coli and 10% of K. pneumoniae strains isolated from children, mostly from urine, were found to bear plasmid-mediated AmpC β-lactamases. Carbapenemase-producing Enterobacteriaceae are less common than ESBL or AmpC producers but their spread is of particular concern. Global frequencies of approximately 4% for K. pneumoniae and <1% for E. coli isolated from children have been reported.

Risk factors for ESBL uropathogens include recurrent UTIs, vesicoureteral reflux, previous exposure to antibiotics, younger age and Klebsiella species. Receipt of antibiotics during the previous 1–3 months, especially as continuous prophylaxis, has been increasingly recognized as a major risk factor for the development of resistant uropathogens. AmpC uropathogens have been associated with previous exposure specifically to third generation cephalosporins as well as underlying conditions requiring hospitalization. Moreover, children with an index UTI by an ESBL or AmpC E. coli or Klebsiella pathogen are at increased risk for a subsequent UTI by the same or different organism with high resistance properties. Risk factors for carbapenemase-producing uropathogens, in particular K. pneumoniae, include prolonged hospitalization, especially in intensive-care settings, invasive medical devices and travel.
to endemic areas.4,6,9 Neonates seem to be a particularly high risk population and these strains often cause outbreaks in neonatal wards, resulting in high rates of morbidity and mortality, and in colonization and UTIs by unusual pathogens months later.10 Rates of ESBL/AmpC-carriers healthy toddlers have been reported to range from 4% to 6.5% in Europe to 23% in Asia.6,9 Apart from healthcare-associated factors, an important role of widespread broad spectrum antibiotics in farming practices has been suggested.4,6

**LABORATORY IDENTIFICATION OF ESBL E. COLI AND K. PNEUMONIAE**

Every *Enterobacteriaceae* uropathogen with resistance or reduced susceptibility to third generation cephalosporins should be tested for ESBL production. ESBL producers hydrolyze third generation cephalosporins but not in the presence of inhibitors such as clavulanic acid.10 Guidance is similar for *E. coli* and *K. pneumoniae* species and is provided by Clinical and Laboratory Standards Institute, European Committee on Antimicrobial Susceptibility Testing and Food and Drug Administration.13 According to recent suggestions, isolated ESBL pathogens are only considered resistant to third generation cephalosporins and not by definition to other β-lactams, such as cefepime or piperacillin-tazobactam, which may retain their activity against community ESBL producers.13 Coreistance to amoxicillin and other β-lactams is well tolerated in children and remains a first-line option for UTIs.3,4 Carbapenemase-producing pathogens have drawn attention to colistin.2 Colistin is well tolerated in children and remains a second line option, but is associated with nephrotoxicity and is prone to emergence of resistance, making the addition of another antibiotic necessary.3

**ANTIMICROBIAL AGENTS FOR ESBL E. COLI AND K. PNEUMONIAE UTIS**

The usual first-line therapeutic choices, that is, penicillins and cephalosporins, are in vitro ineffective against ESBL-producing *E. coli* and *K. pneumoniae* strains, and coreistance to other agents narrows further the therapeutic armamentarium. Carbapenems are the most reliable, and in severe cases, the only, treatment option; however, their judicious use is needed to avoid development of carbapenemase-producing pathogens. Given the limited development of novel agents for resistant Gram-negative pathogens, alternatives have been sought among commonly used and overlooked antibiotics with potential activity.3,6

**Commonly Used Antibiotics**

Piperacillin-tazobactam, cefepime, aminoglycosides, trimethoprim-sulfamethoxazole and quinolones might be effective and can be considered as empirical therapy.4 Coreistance to aminoglycosides is common, but amikacin may remain active.5,7 Piperacillin-tazobactam and cefepime may retain their activity, especially against community ESBL *E. coli* but not against *K. pneumoniae* strains.11,17 Both agents often show false activity against strains with multiple resistance mechanisms or might render ineffective in cases with high bacterial inoculum,16 such as children with bacteremic UTIs or those who bear medical devices. For these reasons, despite the new recommendations, some laboratories still report ESBL pathogens as resistant to piperacillin-tazobactam and cefepime even if susceptible in vitro.16 Trimethoprim-sulfamethoxazole and quinolones, if active, are excellent options for children who can be treated orally. Aminoglycosides and quinolones remain first-line options in children who can be treated orally. Aminoglycosides and quinolones remain first-line choices in combination regimens for carbapenemase-producing strains.16

**Re-emerging Agents**

Some unique class older antibiotics such as fosfomycin and nitrofurantoin have retained their activity against ESBL *E. coli* and *K. pneumoniae* and re-emerged as options for UTIs.3,4,16 Data for children are limited, but these agents seem worth of consideration especially for non–life-threatening infections.3,4 The oral formulation of fosfomycin is particularly appealing for treatment continuation after initial improvement. Nitrofurantoin could only be an option for cystitis, given its insufficient serum levels and minimal parenchymal penetration.16 There are efficacy data for extended spectrum penicillin derivatives, such as piperacillin or piperacillin-tazobactam in uncomplicated UTIs in children, but these agents are not widely available.3,4 Carbapenemase-producing pathogens have drawn attention to colistin.2 Colistin is well tolerated in children and remains a second line option, but is associated with nephrotoxicity and is prone to emergence of resistance, making the addition of another antibiotic necessary.3

**Carbapenems**

Carbapenems with their excellent in vitro activity are reserved for children with severe clinical presentation or nosocomial infection. Most of the experience in pediatrics is with imipenem or meropenem,9,16 but recent reports have highlighted the use of ertapenem particularly in UTIs.4 Carbapenemase production does not necessarily translate to treatment failure and in such cases combination therapy is recommended, based on meropenem minimal inhibitory concentration (MIC) in susceptibility testing.9,16 Carbapenem-containing combination regimens are associated with more favorable outcomes in cases with relatively low MIC (<8 mg/L) and meropenem given as a prolonged infusion.9,16

**Novel and Emerging Agents**

Tigecycline, a semisynthetic tetracycline, is among the newest agents against Gram-negative pathogens; however, its role in UTIs is doubtful due to limited renal excretion and its use is discouraged for children younger than 8 years of age due to permanent teeth discoloration.9 Agents in development include combinations of cephalosporins with newer β-lactamase inhibitors, novel carbapenems and aminoglycosides, and ceftazidime-avibactam and ceftolozane-tazobactam are being investigated in children with complicated UTIs caused by multiresistant organisms.3,16,18

**CONSIDERATIONS FOR TREATMENT CHOICES**

The choice of the optimal regimen for ESBL *E. coli* and *K. pneumoniae* UTIs is often challenging and should be based on disease severity and susceptibility testing.4

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**TABLE 1. Clinically Important β-lactamases Produced by Resistant *Escherichia coli* and Klebsiella pneumoniae Uropathogens**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Bush-Jacoby-Medeiros Classification</th>
<th>Mechanism of Resistance</th>
<th>Representative enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>2be, 2br, 2ber 2f</td>
<td>ESBLs</td>
<td>TEM, SHV, CTX-M</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbenapemases</td>
<td><em>K. pneumoniae</em> carbenapemase (KPC)</td>
</tr>
<tr>
<td>Class B</td>
<td>3a, 3b</td>
<td>Carbenapemases (metallo-β-lactamases)</td>
<td>VIM, IMP, NDM</td>
</tr>
<tr>
<td>Class C</td>
<td>1</td>
<td>Plasmid-mediated cephalosporinas (AmpC)</td>
<td>CMY, FOX, ACT</td>
</tr>
<tr>
<td>Class D</td>
<td>2df</td>
<td>Penicillinas and carbenapemases</td>
<td>OXA</td>
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</tbody>
</table>
According to our interpretation of available data (Fig. 1), risk factors for ESBL infection should be taken into account for the choice of initial agents, but this does not necessarily involve the use of carbapenems for every child. Noncarbapenem agents, such as amikacin and piperacillin-tazobactam, could be used for initial empirical treatment of uncomplicated, community-acquired infections, as adequate disease control without adverse long-term outcomes has well been reported for children with pyelonephritis from ESBL-producing organisms.2,10,16,22 Despite in vitro resistance, empirical treatment with ceftriaxone was successful against ESBL E. coli pyelonephritis and was maintained as definitive treatment in one study.22

An important issue that has not been adequately addressed is whether treatment modification according to susceptibility testing is required in patients who have already responded clinically and microbiologically to initial treatment. A few studies that have addressed this issue in children with ESBL E. coli and K. pneumoniae UTIs suggested that clinical and microbiologic response is achieved despite inappropriate treatment according to susceptibility tests.2,10,16,22 These results are potentially explained by the higher concentrations of the drugs in the urine than those achieved systemically.1,4,16 However, these findings should be interpreted with caution due to very small sample sizes and study limitations. While it appears that susceptibility testing cannot always predict outcomes, there is still not enough evidence suggesting that antibiotics can be used as treatment regardless of susceptibility results.

UTIs by resistant E. coli and K. pneumoniae do not pose a greater risk for recurrences or permanent renal lesions, as shown in comparative studies.17,19,21; hence prolonged intravenous or overall treatment is not required. However, longer hospitalization may be required due to limited options for oral treatment.4 Oral agents, such as trimethoprim-sulfamethoxazole, fosfomycin or nitrofurantoin, might be of use for this purpose, as well as for afebrile cases of cystitis.4,16

Carbapenems should be reserved for severe clinical presentation, suspicion of bacteremia and complicated urologic history.4,16 For carbapenemase-producing strains, carbapenem-containing combination treatment is recommended with a second effective agent (Fig. 1).16 In exceptional cases with high MIC carbapenem resistance, colistin-based combination therapy might be required as a last-resort option.16

CONCLUSIONS

The rates of ESBL E. coli and K. pneumoniae as UTI pathogens are increasing even in community-acquired infections. Risk factors in children, especially recent or current exposure to antibiotics, have been adequately identified and should be taken into account in treatment decisions. Although carbapenems remain the cornerstone of treatment in more severe cases, alternative agents are worth of consideration in uncomplicated UTIs. Well-designed clinical outcome studies will contribute to the formulation of appropriate therapeutic guidelines for these infections.

REFERENCES


