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# Oral and Parenteral Therapeutic Options for Outpatient Urinary Infections Caused by *Enterobacteriaceae* Producing CTX-M Extended-Spectrum β-Lactamases▽

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**Effective therapeutic options are needed for community-onset urinary tract infections due to *Escherichia coli* strains that produce CTX-M extended-spectrum β-lactamases. We examined 46 urinary isolates producing CTX-M against several oral or long-acting parenteral antimicrobial agents. Approximately 90% were susceptible to fosfomycin and to a combination of cefdinir plus amoxicillin-clavulanate. All were susceptible to ertapenem.**

Since the early 1990s, *Escherichia coli* isolates that produce CTX-M extended-spectrum β-lactamases (ESBLs) have emerged as a serious cause of urinary tract infections (UTIs) in the community (18). Mortality in the more severe infections, particularly those progressing to bacteremia, is as high as 60.8% (14). Chances of survival increase with appropriate initial antibiotic coverage, while delay in proper therapy is associated with increased mortality (14). Empirical antibiotic therapy, particularly in the outpatient setting, is problematic as most of these organisms are resistant to fluoroquinolones, trimethoprim-sulfamethoxazole, oral cephalosporins, and amoxicillin-clavulanate (18, 22). The primary goal of this investigation was to identify potential treatment options for outpatient UTIs with these organisms. We tested several candidate oral antibiotics and one long-acting parenteral agent against a collection of genetically characterized ESBL-producing isolates.

The ESBLs produced by each isolate were characterized by PCR amplification followed by sequencing of PCR products as previously described (13). A total of 45 UTI isolates (predominantly *E. coli*) that produced a CTX-M alone (40 producing CTX-M15, three producing CTX-M16, and one each producing CTX-M8 and CTX-M14) and one isolate that produced a CTX-M15 and an SHV-2 ESBL were examined along with 11 isolates that produced only SHV (four producing SHV-12, three producing SHV-2, and three producing SHV-5) or TEM-10 ESBLs. All isolates were recovered between 2002 and 2008. Isolates were stored frozen at −70°C in skim milk and subcultured twice prior to susceptibility testing. Each isolate was tested for susceptibility to fosfomycin by the CLSI agar dilution method (4) and to ciprofloxacin, doxycycline, ertapenem, and nitrofurantoin and to a novel combination of cefdinir plus a fixed concentration of amoxicillin-clavulanate by the CLSI broth microdilution method (4). For testing the unique combination of cefdinir and amoxicillin-clavulanate, the cefdinir was diluted in the usual twofold dilution scheme in a fixed concentration of 8 μg/ml amoxicillin and 4 μg/ml clavulanate. Both cefdinir and amoxicillin-clavulanate were tested separately in the normal twofold dilution format to ascertain their activities when tested alone. The calculation of the percentage of isolates susceptible to the three-drug combination was based upon the cefdinir component and use of the approved cefdinir-susceptible breakpoint of ≤1 μg/ml (5).

Results are summarized in Table 1. Approximately 90% of urinary CTX-M ESBL-producing isolates were susceptible to the combination of cefdinir plus amoxicillin-clavulanate and to fosfomycin. One hundred percent of isolates were susceptible to ertapenem. Nitrofurantoin was active against 73.9% of isolates, while only 10.9% and 4.3% were susceptible to doxycycline and ciprofloxacin, respectively. Testing of the 11 SHV or TEM ESBL-producing strains showed similar results, with the exception of nitrofurantoin, to which a majority were resistant (Table 2).

*E. coli* strains that produce CTX-M ESBLs, primarily found in community sources, are becoming widely prevalent worldwide, most notably in Europe and Canada (16, 17, 18). The emergence of community-onset UTIs in particular is concerning as they are mostly resistant to oral antibiotics (3, 7, 8, 13, 22, 23, 25). One study from Spain reported a threefold rise in community-onset UTIs caused by ESBL-producing *E. coli* over a 3-year period, most of which were also resistant to trimethoprim-sulfamethoxazole and fluoroquinolones (3). Another study from the United Kingdom revealed a similar trend in which 24% of 291 CTX-M-producing *E. coli* isolates (mostly urinary in origin) came from the community, most of them also being resistant to fluoroquinolones, trimethoprim-sulfamethoxazole, and tetracycline (25). Resistance to commonly prescribed oral antibiotics leads to inadequate empirical therapy and potentially the development of more severe infections including bacteremia. One study showed that with ESBL-producing *E. coli* strains isolated from nonhospitalized patients

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TABLE 1. $MIC_{50}$s, $MIC_{90}$s, and percent susceptibilities of urine CTX-M ESBL-producing isolates to the study antimicrobial agents

| Drug | Value for CTX-M ESBL-producing isolates ($n$ = 46) | | |
|---|---|---|---|
| | $MIC_{50}$ (μg/ml) | $MIC_{90}$ (μg/ml) | % Susceptible |
| Fosfomycin | 0.5 | 64 | 91.3 |
| Nitrofurantoin | 16 | 64 | 73.9 |
| Doxycycline | 16 | 16 | 10.9 |
| Ciprofloxacin | 32 | 32 | 4.3 |
| Cefdinir alone | 16 | 16 | 0 |
| Amoxicillin-clavulanate alone | 32/4 | 32/4 | 10.9 |
| Cefdinir plus amoxicillin-clavulanate | 0.25[a] | 2[a] | 89.1 |
| Ertapenem | 0.06 | 0.25 | 100 |

[a] Cefdinir MIC in the presence of a fixed concentration of 8 μg/ml amoxicillin and 4 μg/ml clavulanate; percent-susceptible value is based upon the approved cefdinir-susceptible breakpoint of <1 μg/ml (5).

TABLE 2. $MIC_{50}$s, $MIC_{90}$s, and percent susceptibilities of urine SHV or TEM ESBL-producing isolates

| Drug | Value for SHV or TEM ESBL-producing isolates ($n$ = 11) | | |
|---|---|---|---|
| | $MIC_{50}$ (μg/ml) | $MIC_{90}$ (μg/ml) | % Susceptible |
| Fosfomycin | 4 | 8 | 100 |
| Nitrofurantoin | 64 | 64 | 45.5 |
| Doxycycline | 16 | 16 | 18.2 |
| Ciprofloxacin | 32 | 32 | 36.4 |
| Cefdinir alone | 4 | 16 | 0 |
| Amoxicillin-clavulanate alone | 32/4 | 32/4 | 45.5 |
| Cefdinir plus amoxicillin-clavulanate | 0.06[a] | 8[a] | 81.8 |
| Ertapenem | 0.12 | 1 | 100 |

[a] Cefdinir MIC in the presence of a fixed concentration of 8 μg/ml amoxicillin and 4 μg/ml clavulanate; percent-susceptible value is based upon the approved cefdinir-susceptible breakpoint of <1 μg/ml (5).

with UTIs, 5 out of 37 patients became bacteremic, requiring hospitalization due to treatment with inadequate initial empirical therapy (22). Another study reported a 4.1% prevalence of community-onset bacteremia caused by ESBL-producing *E. coli* with an associated mortality rate of 21.1% (9).

The rise in community-onset UTIs with ESBL-producing *E. coli* strains raises the question of how to treat these infections effectively on an outpatient basis. A recent case control study reported a 93% cure rate for cystitis using amoxicillin-clavulanate for community-onset UTIs with ESBL-producing *E. coli* strains that were susceptible to that combination. However, 29% of the isolates were resistant to amoxicillin-clavulanate (21). Our study revealed that, while no isolates were susceptible to cefdinir alone and only 10.9% of isolates were susceptible to amoxicillin-clavulanate alone, the addition of a fixed concentration of amoxicillin-clavulanate to cefdinir raised the percentage of isolates susceptible to 89.1% based upon a MIC of ≤1 μg/ml of cefdinir in the presence of the β-lactamase inhibitor combination. We reason that the clavulanate component of amoxicillin-clavulanate served to inhibit the ESBL, resulting in effective cefdinir activity against most isolates. Clavulanate is very effective in inhibiting ESBLs in vitro (15). In fact, phenotypic detection of ESBLs involves testing of substrate drugs (i.e., cefotaxime and ceftazidime) alone and in the presence of a fixed concentration of clavulanate (5). Markedly increased susceptibility in the presence of the β-lactamase inhibitor provides phenotypic evidence of the production of an ESBL. Cefdinir is an oral extended-spectrum cephalosporin with activity against many members of the *Enterobacteriaceae*, resists hydrolysis by several common β-lactamases, and has excellent urinary penetration (2, 6). Uncomplicated UTIs due to non-ESBL-producing strains treated with cefdinir resulted in a 91.3% clinical cure rate in one study (12). Clavulanate is not available for administration by itself, but coadministration of amoxicillin-clavulanate with cefdinir represents a theoretically attractive option for oral therapy of UTIs due to ESBL-producing organisms. Both cefdinir and amoxicillin-clavulanate achieve high drug levels in urine (amoxicillin-clavulanate and cefdinir package inserts [http://dailymed.nlm.nih.gov/dailymed/about.cfm]).

Another promising option is fosfomycin, which inhibited 91.3% of the urine CTX-M ESBL-producing isolates in this study. Fosfomycin, a derivative of phosphonic acid, targets bacterial cell wall synthesis. It is well tolerated and can be administered as a once-daily dose (10). The drug's excellent urinary penetration and the rarity of resistance to it in clinical isolates also make it an appealing option for treating outpatient UTIs (11, 20).

Ertapenem, a long-acting parenteral carbapenem, was active against 100% of CTX-M- and SHV- or TEM-producing isolates in this study. A previous study revealed 100% susceptibility to ertapenem of ESBL-producing *Enterobacteriaceae* (including *E. coli*, *Proteus mirabilis*, and *Klebsiella* species) isolates causing community-onset urinary infections with only slight increases in the $MIC_{50}$ for strains that produced ESBLs (0.03 μg/ml) compared to that for strains that did not produce an ESBL (0.015 μg/ml) (1). Another study in which outpatient urinary ESBL-producing *E. coli* isolates retained 100% susceptibility to ertapenem (with a $MIC_{90}$ of 0.06 μg/ml) supports our findings as well (24). Ertapenem's stability to hydrolysis by several β-lactamases; its long half-life, which allows for once-daily dosing; and its ability to concentrate in the urine make it another potential option for outpatient therapy (24).

Appropriate outpatient treatment options targeting urinary ESBL-producing *E. coli* strains are increasing in importance. The correct choice of empirical and targeted antibiotic therapy is especially important in preventing progression to more serious infections such as bacteremia, which is associated with increased mortality. Further, it is important that laboratories test for ESBL producers from outpatient urine cultures and test relevant drugs to assist with culture-directed therapy of proven infections due to ESBL producers. Our data indicate that the novel cefdinir-plus-amoxicillin-clavulanate combination, fosfomycin, and the once-daily carbapenem ertapenem are promising treatment options for outpatient UTIs due to CTX-M ESBL-producing *E. coli* strains. Clinical studies are needed to explore the utility of these treatment options.

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