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Oral Treatment Options for Ambulatory Patients with Urinary Tract Infections Caused by Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*▽

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An increase in extended-spectrum-β-lactamase (ESBL)-producing *Escherichia coli* has been observed in outpatient settings. Consequently, 100 ESBL-positive *E. coli* isolates from ambulatory patients with clinically confirmed urinary tract infections were collected by a single laboratory between October 2004 and January 2008. Antimicrobial susceptibility testing was carried out using the oral antibiotics fosfomycin, pivmecillinam, and nitrofurantoin and the parenteral antibiotic ertapenem. Susceptibility rates indicate that fosfomycin (97%), nitrofurantoin (94%), and pivmecillinam (85%) could be considered important oral treatment options.

Escherichia coli is the most common pathogen of bacterial infections worldwide. As many as 80% of urinary tract infections (UTIs) are caused by *E. coli.* In 1980, resistance to extended-spectrum cephalosporins was found for the first time in *Enterobacteriaceae* showing no chromosomally encoded AmpC overexpression. This newly detected plasmid-encoded resistance was selected by the frequent use of cephalosporins. These bacterial enzymes have been named extended-spectrum β-lactamases (ESBL) due to their capacity to inactivate practically all cephalosporins (21). ESBL-producing phenotypes of the family of *Enterobacteriaceae* were primarily considered multiresistant organisms originating in hospitals. In recent years, an increase of such ESBL producers has been observed in outpatient settings, especially related to UTIs, reducing the treatment options to a limited number of antibiotics (2, 3, 9, 14, 21). Of special concern are associated coresistances to other classes of antimicrobials, which aid the spreading of multiresistant isolates (12). CTX-M β-lactamase-producing *Enterobacteriaceae*, which are commonly found in outpatients and isolated from UTIs, are typically also resistant to quinolones, aminoglycosides, and sulfonamides, such as ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole, respectively (10, 16).

The aim of our study was to evaluate antimicrobial agents which can be used in outpatient health care for the treatment of uncomplicated and complicated UTIs caused by ESBL-producing *E. coli*. For this purpose, we analyzed susceptibility rates of *E. coli* isolates from clinically significant UTIs to fosfomycin, pivmecillinam, nitrofurantoin, and ertapenem.

Fosfomycin is a phosphor acid derivative produced by *Streptomyces* spp. It inhibits bacterial cell wall synthesis and impairs the adherence to urogenital mucosa. Stabilized with tromethamine, it can be orally administered as a single dose of 3 g for the treatment of UTIs (17). It is well tolerated, with negligible side effects, such as diarrhea and headache, and is applicable during pregnancy (6, 7).

Pivmecillinam is a β-lactam antibiotic which works specifically on *Enterobacteriaceae* by binding to penicillin-binding protein 2 and inhibiting the bacterial cell wall synthesis. An orally administered, twice-a-day dose of 400 mg is recommended for the treatment of UTIs (8).

Nitrofurantoin is a bactericidal drug. It is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. A 7-day, twice-daily administration of 100 mg is recommended (http://www.drugs.com/pro/nitrofurantoin-capsules.html).

Ertapenem is a broad-spectrum β-lactam antibiotic that can be administered only parenterally, but it has a long half-life, allowing for a treatment dose of 1 g per day in outpatient health care (22).

ESBL-producing *E. coli* isolates (n = 100) were collected consecutively (October 2004 to January 2008) from clinically certified UTIs. Ninety-eight specimens were submitted by attending general practitioners, while only two were derived from hospitals. Limited information was available concerning patients' previous treatment with antibiotics, previous hospitalization, or risk factors for urinary tract infections. Patients' ages ranged from 2 to 97 years (average mean age, 57.6 years). Seventy-eight percent of isolates derived from female patients, and 22% derived from male patients. Seven isolates came from patients in long-term-care facilities.

E. coli isolates (n = 6,066) from UTIs with resistance to one or more antimicrobial agents were screened (Table 1). Resistance testing was carried out with the Vitek 2 system and the AST-N020 card (bioMerieux, Marcy l'Etoile, France) according to the manufacturer's instructions. Isolates were considered presumptive ESBL producers when they exhibited MICs of cefotaxime, cefpodoxime, and ceftazidime that were ≥2 μg/ml. ESBL expression was confirmed by means of the double-disk synergy test with commercially available discs (Oxoid, Basingstoke, United Kingdom) according to 2007 CLSI guide-

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TABLE 1. Proportions of ESBL-producing *E. coli* isolates susceptible to the antimicrobial agents examined

Yr	No. of *E. coli* isolates from urine	No. of ESBL-producing *E. coli* isolates (%)	% (no.) of ESBL-producing *E. coli* isolates susceptible to[a]:						
			FOF	MEL	ETP	NIT	SXT	GEN	CIP
2005	1,809	18 (0.99)	94.44 (18)	88.88 (18)	100 (18)	88.88 (18)	33.33 (18)	72.22 (18)	27.77 (18)
2006	1,995	28 (1.40)	96.43 (28)	96.43 (28)	100 (28)	96.43 (28)	28.57 (28)	78.57 (28)	7.14 (28)
2007	2,262	44 (1.94)	100 (44)	79.54 (44)	100 (19)	93.18 (44)	22.73 (44)	79.54 (44)	29.54 (44)
Total	6,066	90 (1.48)	97 (100)[b]	85 (100)[b]	100 (66)	94 (100)[b]	27 (100)[b]	78 (100)[b]	22 (100)[b]

[a] FOF, fosfomycin; MEL, pivmecillinam; ETP, ertapenem; NIT, nitrofurantoin; GEN, gentamicin; SXT, trimethoprim-sulfamethoxazole; CIP, ciprofloxacin.
[b] Ninety isolates (from 2005 to 2007) plus 10 from 2004 and 2008.

lines (4). All verified ESBL-producing strains ($n = 100$) were tested for pivmecillinam, fosfomycin, and ertapenem. Susceptibility testing for all three substances was carried out with the agar diffusion test and the Etest. All results were evaluated according to the 2007 CLSI guidelines (4).

Susceptibility results for gentamicin, nitrofurantoin, trimethoprim-sulfamethoxazole, and ciprofloxacin were taken retrospectively from the Vitek 2 resistance data mentioned above.

A 97% susceptibility to fosfomycin ($n = 100$ isolates) was determined by both methods (Table 1). The susceptible isolates exhibited very low MICs, as determined by the Etest, with a mean value of 1.38 μg/ml.

Results of the efficacy of pivmecillinam varied. The susceptibility rate as determined by the agar diffusion test was 77%, and 10% of isolates were classified as having reduced susceptibility. The susceptibility rate to pivmecillinam as determined by the Etest was 85%, and 4% of the isolates showed reduced susceptibility (Table 1). The mean value of the MICs as determined by the Etest was 1.17 μg/ml.

Isolates exhibited 94% susceptibility to nitrofurantoin, and 5% of the isolates were classified as intermediate (Table 1). MICs of susceptible isolates had a mean value of 17.02 μg/ml. These results were obtained from Vitek 2.

We found no resistance against ertapenem in all tested ($n = 66$) isolates (Table 1). The MICs as determined by the Etest had a mean value of 0.07 μg/ml.

The study of further resistances by means of the evaluation of antibiograms revealed a susceptibility rate of 78% to gentamicin, 27% to trimethoprim-sulfamethoxazole, and 22% to ciprofloxacin (Table 1).

These *in vitro* results indicate a high β-lactamase stability of pivmecillinam against ESBL-producing *E. coli*. The clinical efficacy of pivmecillinam was affirmed recently by a case study (13).

The high *in vitro* activity of fosfomycin renders this substance an alternative oral treatment option of UTIs associated with ESBL-producing *E. coli*. These susceptibility data have also been demonstrated by de Cueto et al., who in 2006 reported a 97.4% susceptibility rate for 428 ESBL-producing isolates (5).

Nitrofurantoin exhibited a high *in vitro* activity which is comparable to the 94.9% susceptibility rate of *E. coli* isolates from 240 recurrent UTIs, as reported in the 2009 Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC) study (18).

None of the 66 isolates tested against ertapenem exhibited an *in vitro* resistance to this antimicrobial agent. These data are congruent with data from Mody et al. (11), Tamayo et al. (20), and Alhambra et al. (1). They reported no resistance of ESBL-producing *E. coli* to ertapenem. The option of using ertapenem once a day makes it a useful parenteral antimicrobial agent for the treatment of serious infections of the urinary tract in nursing homes and outpatient health care settings (15).

The evaluation of coresistances revealed a high rate of resistance mechanisms to aminoglycosides, quinolones, and sulfonamides in ESBL-producing *E. coli*. Ciprofloxacin and trimethoprim-sulfamethoxazole, with resistance rates of >70%, must be ruled out as therapy options for the treatment of UTIs caused by ESBL-producing organisms. Schwaber et al. examined 70 ESBL-expressing *E. coli* isolates and detected >80% resistance to the agents mentioned above (19). Also, the administration of gentamicin, with a resistance rate of 21%, is not indicated for the treatment of ESBL-associated UTIs. This rate is slightly lower than the 27% resistance rate Alhambra et al. found in 315 multiresistant *E. coli* isolates causing UTIs (1).

Based on our recent data, fosfomycin, nitrofurantoin, and pivmecillinam could be considered important oral treatment options for ambulatory patients with UTIs caused by ESBL-producing *E. coli*. Ertapenem is a highly efficient antibiotic which could be used for the treatment of complicated UTIs in long-term-care facilities (15).

These *in vitro* data have yet to be confirmed by further clinical studies.

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