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ESBL Producing *Escherichia coli* in ambulatory Urinary Tract Infections - Oral Treatment Options?

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

Escherichia coli is the most common pathogen of bacterial infections worldwide. As many as 80% of urinary tract infections are caused by *E. coli.* In 1980, resistance to third class cephalosporines was found for the first time in *Enterobacteriaceae* showing no chromosomal-coded AmpC overexpression. This newly detected plasmid-encoded resistance was selected by the frequent use of cephalosporines. These bacterial enzymes have been named Extended-Spectrum-Beta-Lactamases (ESBL) due to their capacity to inactivate practically all cephalosporines (21). ESBL-producing phenotypes of the family of *Enterobacteriaceae* were primarily considered as multiresistant organisms originating in hospitals. In the recent years, an increase of such ESBL-producers has been observed in outpatient settings, especially related to urinary tract infections (UTI), 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 ß-lactamases producing Enterobacteriaceae, which are commonly found in outpatients and isolated from UTIs, are typically also resistant to quinolones, aminoglycosides and sulfonamides such as ciprofloxacine, gentamicin and trimethoprim/sulfamethoxazole, respectively (10, 16).

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

Fosfomycin is a phosphoracid- derivative produced by *Streptomyces sp.* It inhibits bacterial cellwall synthesis and impairs the adherence to urogenital mucosa. Stabilized "with Tromethamine it can be orally administered as a single-dose of 3g for the treatment of UTIs (17). It is well tolerated with neglectable side effects like diarrhea and headache and is applicable during pregnancy (6,7).

Mellicinam is a ß-lactam antibiotic which works specificly on *Enterobacteriaceae* by binding to penicillin-binding protein 2 and inhibiting the bacterial cellwall 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 (23)

Ertapenem is a broadspectrum ß-lactam antibiotic that can only be administered parenterally, but it has a long half-life allowing a 1g-per-day-dose treatment in outpatient healthcare (22).

100 ESBL-producing E. coli isolates were collected consecutively (October 2004 to January.2008). from clinically certified UTIs. 98 specimens were submitted by attending general practitioners while only 2 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 (avg.mean age, 57.6 years). 78% isolates derived from female and 22% from male patients. 7 isolates came from patients in long-term care facilities.

8416 *E. coli* isolates from UTIs with resistance to one or more antimicrobial agents were screened [Table1]. 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 as presumptive ESBL-producers when they exhibited minimum inhibitory concentration (MICs) of cefotaxime, cefpodoxime and ceftazidime ≥ 2µg/mL. ESBL-expression was confirmed by means of the double disk synergy test with commercial available discs (Oxoid, Basingstoke, UK) according to CLSI guidelines 2007 (4). All verified ESBL-producing strains (n=100) were tested for mecillinam, fosfomycin and ertapenem. Susceptibility testing for all three substances was carried out with the agar diffusion test and the E-Test. All results were evaluated according to the CLSI guidelines 2007 (4).

Susceptibility results for gentamicin, nitrofuratoine, trimethoprim/sulfamethoxazole and ciprofloxacin were taken retrospectively from VITEK 2 resitance data mentioned above.

A 97% susceptibility to fosfomycin (n=100) was determined in both methods [Table1]. The susceptible isolates exhibit very low MICs in E-test with a mean value of 1.38 µg/mL.

Results in the efficacy of mecillinam varied. Agar diffusion test susceptibility rate was 77% and 10% of isolates were classified as isolates with reduced susceptibility. The susceptibility rate of mecillinam in the E-test was 85% and 4% of the isolates showed reduced susceptibility [Table1]. Mean value of MICs in E-test was 1.17 µg/mL.

Nitrofurantoin exhibited 94% susceptibilty and 5% were classified as intermediate [Table1]. MICs of susceptible isolates had a mean value of 17.02 µg/ml. These results were obtained from VITEK2.

We found no resistance against ertapenem in all tested (n=66) isolates [Table1]. The MICs in E-test had a mean value of 0.07 µg/mL.

The study of further resistances by means of the evaluation of antibiograms revealed a susceptibilty rate of 78% for gentamycine, 27% for trimethoprim/sulfamethoxazole and 22% for ciprofloxacine [Table1].

These in-vitro results indicate a high β-lactamase stability of mecillinam against ESBL-*E.coli*. The clinical efficacy of mecillinam 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*. This susceptibility data has also been demonstrated by de Cueto et al, who in 2006, reported a 97,4% susceptibility rate in 428 ESBL-producing isolates (5).

Nitrofurantoin exhibited a high in-vitro activity which is comparable to the 94,9% susceptible *E.coli* isolated from 240 recurrent UTIs in the ARESC study 2009 (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, Tamayo et al and Alhambra et al. They reported no resistance of ESBL-producing *E. coli* to ertapenem (1,11,20). 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 healthcare settings (15).

The evaluation of coresistances revealed a high rate of resistance mechanisms to aminoglycosids, quinolons and sulfonamids in ESBL-producing *E. coli*. Ciprofloxacine and trimethoprim/sulfamethoxazole with a resistance rate >70%, must be ruled out as a therapy option for the treatment of UTIs caused by ESBL-producing organisms. Schwaber et al, examined 70 ESBL-expressing *E. coli* and detected >80% resistance to the agents mentioned above (19). Also the administration of gentamicine with a resistance rate of 21% is not indicated for the treatment of ESBL-associated UTIs. This rate is slightly lower than the 27%

resistant isolates Alhambra et al, found in 315 multiresistant E. coli causing UTIs (1).

Based on our recent data fosfomycin, nitrofurantoin and mecillinam could be considered as important oral treatment options in ambulatory 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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Table1: Proportions of ESBL-producing E. coli isolates susceptible to the antimicrobial agents examined[a]

	No. of Isolates of urine E.coli	No. of ESBL-producing E.coli (%)	% (No. of ESBL-E.coli) of isolates susceptible to:						
			FOF	MEL	ETP	NIT	SXT	GEN	CIP
2005	1809	18 (0.99)	94.44% (n=18)	88.88% (n=18)	100% (n=18)	88.88% (n=18)	33.33% (n=18)	72.22% (n=18)	27.77% (n=18)
2006	1995	28 (1.40)	96.43% (n=28)	96.43% (n=28)	100% (n=28)	96.43% (n=28)	28.57% (n=28)	78.57% (n=28)	7.14% (n=28)
2007	2262	44 (1.94)	100% (n=44)	79.54% (n=44)	100% (n=19)	93.18% (n=44)	22.73% (n=44)	79.54% (n=44)	29.54% (n=44)
Total	6066	90 (1.48)	97% [b] (n=100)	85% (n=100)	100% (n=66)	94% (n=100)	27% (n=100)	78% (n=100)	22% (n=100)

[a] FOF, Fosfomycin; MEL, Mecillinam; ETP, Ertapenem; NIT, Nitrofuratoine; GEN, Gentamicin; SXT, Trimethoprim-Sulfamethoxazole; CIP, Ciprofloxacin.

[b] (n = 100) result from 90 isolates (2005-2007) + 10 from 2004 and 2008