

ESBL PRODUCING ESCHERICHIA COLI IN UNCOMPLICATED URINARY TRACT INFECTIONS – ORAL TREATMENT OPTIONS?

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ABSTRACT:

In recent years an increase of infections with *Extended-Spectrum-Beta-Lactamase (ESBL)-producers* has been observed in outpatient treatment of urinary tract infections (UTI) thereby reducing the treatment options to limited classes of antibiotics. This in-vitro study was conducted as to evaluate potential oral antibiotic UTI treatment options in the ambulant setting. 100 *ESBL-positive Escherichia coli*-isolates were collected consecutively from clinically confirmed UTI's of non-hospitalized patients of a single laboratory over a period of three years and four months (October 2004 to January 2008). Resistance testing was carried out by means of the agar diffusion test and the epsilometer test (E-test) using the oral antibiotics Fosfomycin and Mecillinam.

Fosfomycin showed a resistance rate of 3% by both methods.

The resistance rate of Mecillinam in the E-test was 11%.

INTRODUCTION:

In the last 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. Of special concern are associated coresistances against other classes of antimicrobials which aid the spreading of multiresistant isolates. CTX-M β -lactamases producing Enterobacteriaceae, which are commonly found in outpatients and isolated from UTI's are typically also resistant to Sulfonamides, Aminoglycosides and Quinolones such as Ciprofloxacin, Gentamicin and Trimethoprim-Sulfamethoxazole, respectively. The aim of our study was to evaluate antimicrobial agents which can be used in outpatient healthcare for the treatment of uncomplicated UTI's caused by *ESBL-producing E.coli*. For this purpose we analysed susceptibility rates of Fosfomycin, Mecillinam and Ertapenem in *E. coli* isolates from clinical significant UTI's.

Fosfomycin is a Phosphoracid - derivate produced by *Streptomyces sp.* It inhibits bacterial cellwall synthesis and impairs the adherence to urogenital mucosa. Stabilized with Tromethamine it can be administered orally as a single-dose for the treatment of UTI's.

Mecillinam is a β -lactam antibiotic which works specific 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 UTI's.

Ertapenem is a broadspectrum b-lactam antibiotic that can only be administered parenterally, but it has a long half-life which allows a 1g per day dose treatment in outpatient healthcare centers.

MATERIAL AND METHODS:

Over a period of three years and 4 months 100 *ESBL-producing E. coli* isolates were collected consecutively from clinically certified UTI's (12. 10. 2004 until 25. 01. 2008). All urine specimens were sent to the laboratory. 98 specimens were sent in from attending general practitioners while only 2 were derived from hospitals.

8416 *E. coli* isolates from urinary tract infections with resistance to one or more antimicrobial agents were screened. Resistance testing was carried out with the VITEK 2-System and the AST-N020 card (bioMérieux, Marcy l'Etoile, France) according to the manufacturer's instructions.

All verified ESBL-producing strains (n=100) were tested for Mecillinam, Fosfomycin and Ertapenem. Susceptibility testing for all three substances was carried out by means of the agar diffusion test and the E-Test. All results were evaluated according to the CLSI guidelines (CLSI 2007).

Results I / Table 1
 Proportions of ESBL-producing *E. coli* isolates susceptible to the antimicrobial agents examined*

	No. of clinical isolates with ≥ 1 resistance	No. of ESBL-producing <i>E. coli</i> (%)	% (No. of ESBL- <i>E. coli</i>) of isolates susceptible to:							
			FOF	MEL	ETP	GEN	SXT	NIT	CIP	
2005	2003	23 (1,15)	94,44% (n=18)	88,88% (n=18)	100% (n=18)	72,22% (n=18)	33,33% (n=18)	88,88% (n=18)	27,77% (n=18)	
2006	2147	31 (1,44)	96,43% (n=28)	96,43% (n=28)	100% (n=28)	78,57% (n=28)	28,57% (n=28)	96,43% (n=28)	7,14% (n=28)	
2007	2438	50 (2,05)	100% (n=44)	79,54% (n=44)	100% (n=19)	79,54% (n=44)	22,73% (n=44)	93,18% (n=44)	29,54% (n=44)	
total			97% (n=100)	85% (n=100)	100% (n=66)	78% (n=100)	27% (n=100)	94% (n=100)	22% (n=100)	

*FOF, fosfomycin; MEL, mecillinam; ETP, ertapenem, GEN, gentamicin; SXT, trimethoprim-sulfamethoxazole; NIT, nitrofurantoin, CIP, ciprofloxacin.

Susceptibility results for Gentamicin, Nitrofurantoin, Trimethoprim-Sulfamethoxazole and Ciprofloxacin were taken retrospectively from routine VITEK 2 resistance data.

RESULTS:

The patients age ranged from 2 to 97 years (mean age of 57,6 years). 78% of isolates derived from female and 22% from male.

In the case of **Fosfomycin** all (n=100) susceptibility results for both methods a resistance rate of 3% was determined (Table 1, Graph 1 and 2). The 97% susceptible isolates exhibit very low MICs in E-test with a mean value of 1.38 μ g/mL (SD \pm 2,39 μ g/mL).

Results for the efficacy of **Mecillinam** (n=100) varied. Agar diffusion test resistance rate was 13% and 10% of isolates were classified as isolates with reduced susceptibility: (Graph 2) The resistance rate of Mecillinam in the E-test was 11% and 4% of the isolates showed reduced susceptibility: (Graph 1) Mean value of MICs in E-test was 1,17 μ g/mL (SD \pm 1,46 μ g/mL).

We found no resistance against **Ertapenem** in all tested (n=66) isolates. The MICs in E-test were low with a mean value of 0,07 μ g/mL (SD \pm 0,09 μ g/mL). (Table 1, Graph 1 and 2)

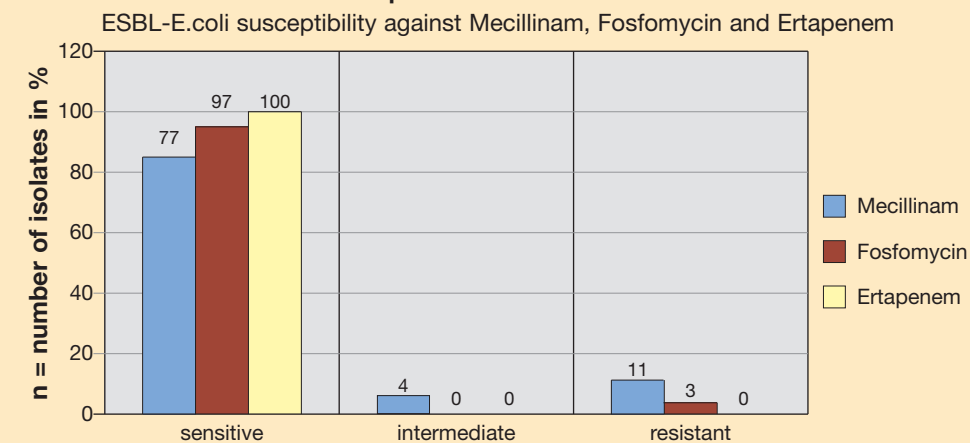
The study of further resistances by means of the evaluation of antibiograms revealed a resistance rate of 27% for Gentamicin, 73% for Trimethoprim/Sulfamethoxazole, 1% for Nitrofurantoin and 78% for Ciprofloxacin. (Table 1, Graph 3)

CONCLUSIONS:

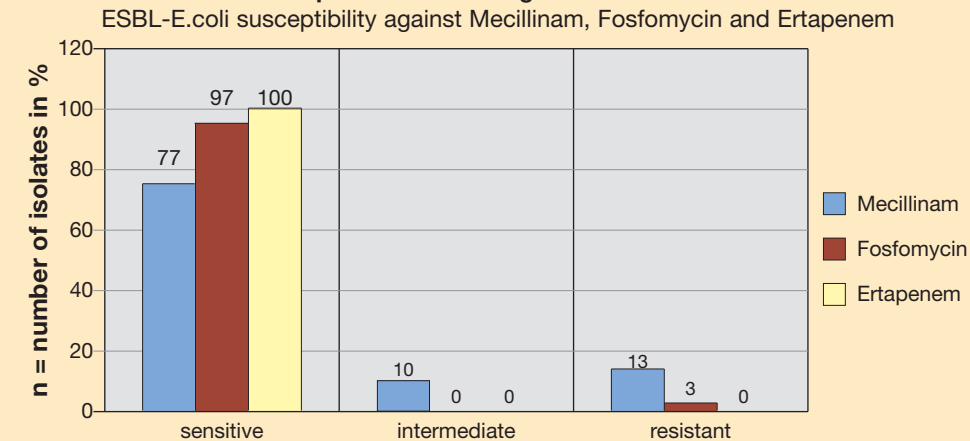
- Fosfomycin can be considered as an alternative option for targeted oral therapy of *ESBL-E.coli* associated UTI's thus dosage and frequency of application remains unclear.
- It may be assumed that Mecillinam is sufficiently safe.
- Ertapenem is a highly efficient antibiotic in these cases, despite the fact it cannot be administered orally.
- This data has only in part been supported by clinical surveys and warrants further studies.

Results II

Graph 1: Results of E-Test



Graph 2: Results of Agar-diffusion-Test



Graph 3: Results of Routine-Testing

