Poster No.

1533

22st ECCMID
London, UK
31 March – 3 April 2012

Occurrence of resistance to fosfomycin in urine isolates of *E. coli* collected from outpatients in Germany, 2010

M. KRESKEN*, B. KÖRBER-IRRGANG on behalf of the Working Party Antimicrobial Resistance of the Paul Ehrlich Society of Chemotherapy

Antiinfectives Intelligence GmbH, Rheinbach, Germany

*Contact information

Michael Kresken, PhD

Antiinfectives Intelligence GmbH
Campus of the University of Applied Sciences

Von-Liebig-Straße 20
53359 Rheinbach
Germany

Fon: + 49-2226-908-912
Fax: +49-2226-908-918

E-mail: michael.kresken@antiinfectives-intelligence.de

Introduction and Purpose

Fosfomycin (FOS) exhibits bactericidal activity against a broad spectrum of aerobic bacteria including *Escherichia coli* (ECO), the leading pathogen responsible for uncomplicated and complicated urinary tract infections (UTI) [1]. The use of FOS for first-line therapy of uncomplicated UTI has attracted increasing attention as there is a lack of cross-resistance (R) between FOS and other classes of antibiotics, including those associated with high or increasing rates of R [2,3].

The objective of this study was to evaluate the susceptibilities of ECO urine isolates to FOS and other oral antibacterial agents commonly used for the treatment of UTI in outpatients.

Methods

Bacterial strains

In a surveillance study conducted between October and December 2010 by the Working Party *Antimicrobial Resistance* of the Paul Ehrlich Society of Chemotherapy, 25 laboratories across Germany were requested each to collect 20 non-duplicate ECO urine isolates.

Identification and susceptibility testing

Preliminary identification of the pathogens was performed by local laboratory methods. Strains were then kept at -70°C and sent to a central laboratory (Antiinfectives Intelligence, Rheinbach, Germany) for susceptibility testing at the end of the collection period. Identification of the species was confirmed using MALDI-TOF. Antimicrobial susceptibility testing was performed using the broth microdilution procedure as described in the DIN ISO document [4] using dry-form microdilution panels purchased from Merlin Diagnostika (Bornheim, Germany). Susceptibility to the following antimicrobial agents was tested: FOS, amoxicillin (AMX), amoxicillin-clavulanic acid (A/C), cefuroxime (CXM), cefixime (CFM), cefpodoxime (CPD), ciprofloxacin (CIP), levofloxacin (LVX), ofloxacin (OFX), norfloxacin (NOR), trimethoprim (TMP), trimethoprim-sulfmethoxazole (SXT) and nitrofurantoin (NIT). MICs were interpreted by EUCAST clinical breakpoints [5]. Clinical breakpoints of FOS were ≤32 mg/l (susceptible, S) and >32 mg/l (R). The CLSI MIC method using ceftazidime +/- clavulanic acid (CLA) and cefotaxime +/- CLA was employed as screening test for ESBL-producing isolates [6]. Multidrug resistant (MDR) isolates were defined as isolates demonstrating resistance to AMX (MIC >8 mg/l) and CPD (MIC >1 mg/l) and non-susceptibility to CIP (MIC >0.5 mg/l).

Data analysis

Data were processed using Microsoft Excel. Statistically significance of differences in R rates was judged by comparing 95%-confidence intervals (CI): If neither rate was contained in the CI of the other one, significance was assumed.

Results

A total of 499 isolates were tested. Isolates were obtained from 428 (85.8%) female and 71 (14.2%) male patients. Patients ranged in age from 1 to 98 yrs (median 59 yrs).

MIC distributions, MIC_{50} and MIC_{90} values as well as the rates of S, intermediate (I) and R isolates obtained with the antimicrobial agents are shown in the **Table.** Overall, R was most common to AMX, A/C, TMP, SXT, and fluoroquinolones and least common to NIT. R to second- and third generation oral cephalosporins varied between 8% and 10%.

Of the 499 isolates, 246 (49.3%) were fully S to the 13 antimicrobials. Further 22 isolates (4.4%) were R to only one drug, which was most commonly AMX (3%). There were 32 isolates (6.4%) meeting the criteria of MDR. Forty isolates with MICs of ≥4 mg/l for CPD were screened for ESBLs, all of which were positive using the confirmatory phenotypic test.

Prevalence of resistance to FOS

Six strains (1.2%) were R to FOS and another 19 had elevated FOS MICs (16-32 mg/l), though rated S. Of these 25 isolates, 17 (68%), 14 (56%), 10 (40%), 7 (28%) and 3 (12%) were R to AMX, A/C, SXT, CIP, and CPD. R to A/C and/or AMX was more frequently distributed among isolates with FOS MICs of ≥16 mg/l than among isolates with FOS MICs of ≤8 mg/l (AMX 68% vs 41.6%, $p<0.01$; A/C 56% vs 31.4%, $p<0.05$). One FOS-R strain and two strains with elevated FOS MICs were R to all drug classes, except NIT.

Conclusions

- **Overall, susceptibility to fosfomycin seems to be very high among *E. coli* urine isolates from outpatients in Germany, as has been observed in other parts of the world [7].**
- **Against a background of an increasing number of isolates that are resistant to various antibiotic classes, fosfomycin-trometamol has been considered as a first-line option for empiric therapy of community-acquired uncomplicated UTI [8].**
- **Prudent use of fosfomycin, however, is mandatory in order to restrict the spread of resistance.**

Table: In vitro activity of fosfomycin and 12 other antibacterial agents against the 499 isolates tested

Antibacterial agent	MIC (mg/l)														MIC_{50} (mg/l)	MIC_{90} (mg/l)	%S	%I	%R
	≤0.063	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512					
Fosfomycin					**293**	129	39	13	14	5	4	1	*1*		≤1	4	98.8	-	1.2
Amoxicillin				**2**	18	114	144	7	5	5	*204*				4	≥64	57.1	-	42.9
Amoxicillin-clavulanic acid					**29**	171	90	46	77	33	26	11	*16*		4	64	67.3	-	32.7
Cefuroxime				2	10	80	262	95	13	*37*					4	8	90.0	-	10.0
Cefixime	**27**	77	213	113	28	5	3	*33*							0.25	1	91.8	-	8.2
Cefpodoxime	**6**	36	242	144	28	3	3	*37*							0.25	1	91.4	-	8.6
Ciprofloxacin	**353**	9	25	9	4	1	6	9	*83*						≤0.063	≥16	79.4	0.8	19.8
Levofloxacin	**348**	8	24	16	5		12	43	*43*						≤0.063	8	80.4	0	19.6
Ofloxacin		**353**	7	19	19	3		12	*86*						≤0.125	≥16	76.0	3.8	20.2
Norfloxacin		**352**	13	28	5	2		2	*97*						≤0.125	≥16	78.8	1.0	20.2
Trimethoprim			**288**	39	7		2	2	4	*157*					≤0.25	≥32	66.9	0.4	32.7
Trimethoprim-sulfmethoxazole			**328**	8	4	3	2		2	*152*					≤0.25	≥32	68.7	0.4	30.9
Nitrofurantoin									**443**	48	4	3	1		≤16	32	99.2	-	0.8

Abbreviations: %-S, % susceptible; %-I, % intermediate; %-R, % resistant; numbers in bold include isolates with MIC < value shown; numbers in italic include isolates with MIC > the highest concentration tested.

References

1. Naber KG et al. (2007) ISBN-13: 978-90-70244-59-0
2. de Cueto M et al. (2006) Enferm Infecc Microbiol Clin 24: 613-6
3. Ko KS et al. (2007) Diagn Microbiol Infect Dis 58: 111-5
4. Deutsches Institut für Normung (DIN) (2006) ISO/FDIS 20776-1:2006
5. EUCAST (2012) http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpointtable_v_2.0_120221.pdf
6. CLSI (2012) M100-S22
7. Raz R (2012) Clin Microbiol Infect 18: 4-7
8. Wagenlehner FM et al. (2011) Urologe A 50: 153-69

Acknowledgements

The authors are grateful to the other members of the study group who contributed to the study: T. Becker (Munich), R. Englert, A. Siedlaczek (Freiburg), F. Hugo (Berlin), S. Burak, A. Gehrt (Düsseldorf), A. Reinecke (Rostock), R. Huber, H. Wisplinghoff, S. Wisplinghoff (Cologne), M. Schröter (Jena), I. Fenner, C. Lensing (Hamburg), U. Knipp, E. Kühnen (Trier), S. Schmitt (Kaiserslautern), M. Jacobs (Dillingen), L. Artz (Ingolstadt), R. Hillert (Görlitz), H. Sahly, W. Hönerlage (Hamburg), E. Gyenes, S. Krämer (Essen), J. Cremer (Kempten), J. Lerner, Dr. U. Thalmaier (Augsburg), A. Eberhard, A. Pranada, F. Pranada (Dortmund), T. Hermann, R. Krajewski (Würzburg), R. Tauchnitz-Hiemisch (Leipzig), R. Schwarz (Mönchengladbach), G. Funke (Ravensburg), P. Finzer (Moers), U. Eigner, M. Holfelder (Heidelberg), J. Enzenauer, J. Esser (Osnabrück)