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Susceptibilities of Gram-negative pathogens from hospitalized patients to colistin and fosfomycin in Germany, 2010

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on behalf of the Working Party Antimicrobial Resistance of the Paul Ehrlich Society of Chemotherapy

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Introduction and Purpose

The treatment of infectious diseases caused by Gram-negative bacteria has increasingly been threatened by the emergence and dissemination of multidrug resistant (MDR) pathogens, like extended-spectrum β-lactamase- (ESBL) or carbapenemase (CASE)-producing Enterobacteriaceae as well as carbapenem-resistant *Acinetobacter* spp. or *Pseudomonas aeruginosa* [1]. Colistin (COL) and fosfomycin (FOS) have been shown to be active against MDR Gram-negative bacteria [2-4].

The objective of this study was to evaluate the susceptibility of clinical isolates of five frequently encountered members of the Enterobacteriaceae family (*Enterobacter* spp., *Escherichia coli, Klebsiella oxytoca, K. pneumoniae, Proteus mirabilis*) as well as of *Pseudomonas aeruginosa* and the *Acinetobacter baumannii* group to COL and FOS in comparison to standard antimicrobial drug classes.

Methods

Bacterial organisms

In a surveillance study conducted between October and December 2010 by the Working Party Antimicrobial Resistance of the Paul Ehrlich Society of Chemotherapy, 21 laboratories across Germany collected 1,888 clinical Gram-negative isolates: *Enterobacter* spp. (n=231), *E. coli* (n=465), *K. oxytoca* (n=117), *K. pneumoniae* (n=240), *P. mirabilis* (n=128), *P. aeruginosa* (n=540) and *A. baumannii* group (n=167).

Susceptibility testing

Susceptibility testing was performed in a central laboratory (Antiinfectives Intelligence). MICs of COL, FOS, ciprofloxacin (CIP), ceftazidime (CAZ), gentamicin (GEN) and meropenem (MEM) were determined by the microdilution method according to the standard ISO 20776-1 [5] and interpreted by EUCAST criteria [6], if available.

Confidence intervals for the differences of resistance rates were evaluated based on Wilson intervals.

Results

Five hundred forty-four (28.8%) and 1,344 (71.2%) isolates were obtained from ICU-patients and from patients on general wards, respectively. Patients ranged in age from <1 to 96 years (median 67 years); the majority of isolates (n=1,068, 56.6%) derived from male patients. Isolates were primarily recovered from respiratory specimens (n=476; 25.2%), wounds (n=464; 24.6%), and urine (n=354; 18.8%).

$MIC_{50/90}$ values as well as the rates of susceptible, intermediate and resistant isolates obtained with the antimicrobial agents are presented in the **Table**.

Of the *E. coli, K. pneumoniae, K. oxytoca* and *P. mirabilis* isolates, 17.6% (n=82), 16.7% (n=40), 13.7% (n=16) and 0.8% (n=1) showed an ESBL-phenotype. Four (1.7%) strains of *K. pneumoniae* harboured a CASE, and of the *A. baumannii* group and *P. aeruginosa* isolates, 19 (11.4%) and 123 (22.8%), respectively, were non-susceptible to MEM. Bacterial strains with one of these resistant types were considered multidrug resistant (MDR). MIC distributions of COL and FOS, comparing the non-MDR and MDR population for each test organism (except *P. mirabilis*), are depicted in the **Figure**.

Resistance to FOS in *E. coli* as well as to COL in *K. pneumoniae* and *A. baumannii* group isolates was more prevalent among the MDR than the non-MDR population (**Figure**). Also, high-level resistance to FOS (MIC >128 mg/L) in *K. pneumoniae, P. aeruginosa* and the *A. baumannii* group was more frequently observed among MDR than non-MDR isolates: *K. pneumoniae* 11.6% vs 4.1%, difference p<0.1; *P. aeruginosa* 52% vs 34.3%, difference p<0.01; and *A. baumannii* group 26.3% vs 6.8%, difference p<0.01 (data not shown).

Conclusions

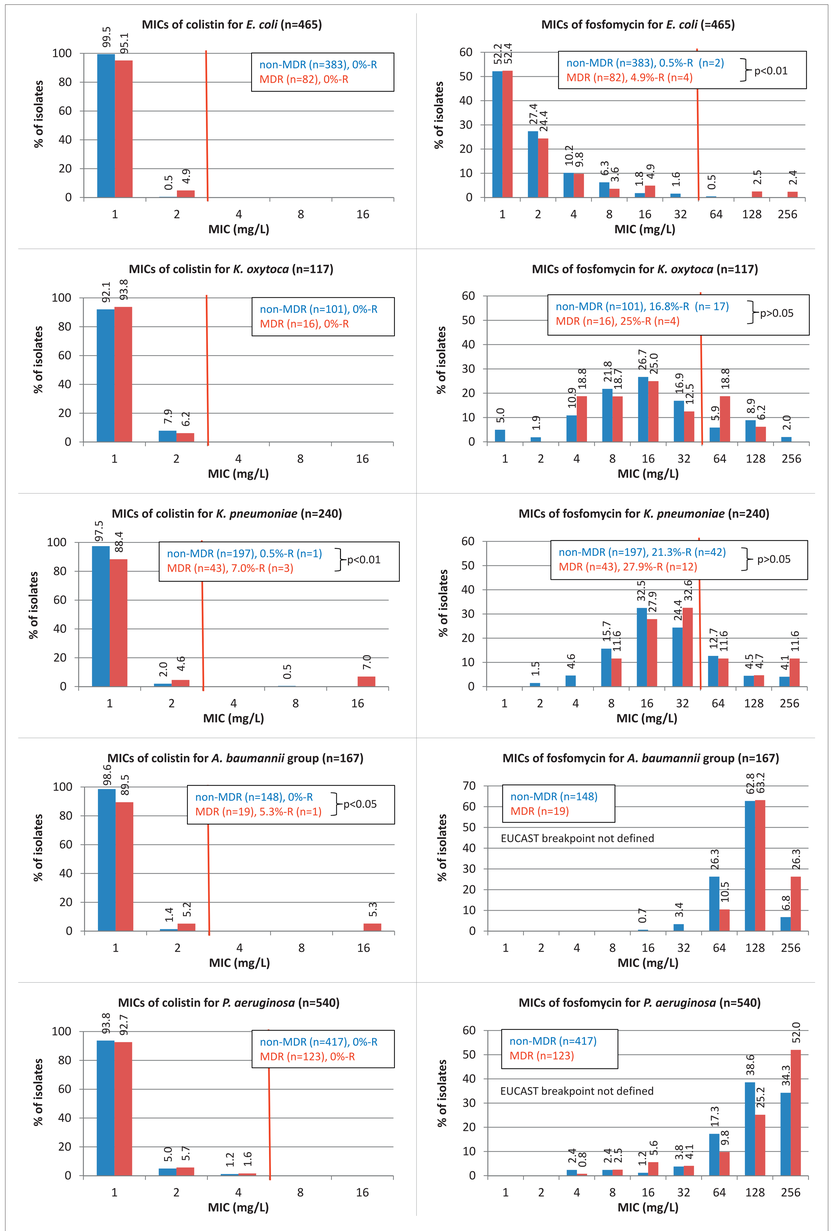
- **Overall, susceptibility to COL was high (90–100%) among all Gram-negative bacteria tested, except naturally resistant *P. mirabilis*.**
- **Susceptibility to FOS was seen in 99% of *E. coli* isolates and appr. 80% of the isolates of the remaining enterobacterial species, except *Enterobacter* spp. (62%).**
- **However, resistance tended to be more widely distributed among MDR isolates than among non-MDR isolates.**
- **Nevertheless, both drugs may play a major role as therapeutic options against MDR Gram-negative bacteria.**

Table: In vitro activity of the test drugs against 1,888 Gram-negative clinical isolates

Isolates (no. tested)	Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R
Enterobacter spp. (231)	Colistin	≤1	2	90.9	–	9.1
	Fosfomycin	32	≥256	61.9	–	38.1
	Ciprofloxacin	≤0.063	0.5	90.9	0.9	8.2
	Ceftazidime	0.5	≥64	68.4	6.1	25.5
	Gentamicin	0.5	1	97.4	1.3	1.3
	Meropenem	≤0.5	≤0.5	99.6	0.4	0.0
E. coli (465)	Colistin	≤1	≤1	100.0	–	0.0
	Fosfomycin	≤1	8	98.7	–	1.3
	Ciprofloxacin	≤0.063	≥16	65.4	1.1	33.5
	Ceftazidime	≤0.25	16	81.9	6.5	11.6
	Gentamicin	1	16	89.2	0.0	10.8
	Meropenem	≤0.5	≤0.5	100.0	0.0	0.0
K. oxytoca (117)	Colistin	≤1	≤1	100.0	–	0.0
	Fosfomycin	16	128	82.1	–	17.9
	Ciprofloxacin	≤0.063	1	88.0	3.4	8.5
	Ceftazidime	≤0.25	1	93.2	6.8	0.0
	Gentamicin	0.5	1	96.6	0.9	2.6
	Meropenem	≤0.5	≤0.5	100.0	0.0	0.0
K. pneumoniae (240)	Colistin	≤1	≤1	98.3	–	1.7
	Fosfomycin	16	64	77.5	–	22.5
	Ciprofloxacin	≤0.063	≥16	78.3	1.7	20.0
	Ceftazidime	≤0.25	32	81.7	0.8	17.5
	Gentamicin	0.5	8	89.2	0.4	10.4
	Meropenem	≤0.5	≤0.5	97.9	0.4	1.7
P. mirabilis (128)	Colistin	≥16	≥16	0.0	–	100.0
	Fosfomycin	8	128	81.3	–	18.8
	Ciprofloxacin	≤0.063	4	79.7	6.3	14.1
	Ceftazidime	≤0.25	≤0.25	97.7	0.8	1.6
	Gentamicin	1	16	86.7	0.8	12.5
	Meropenem	≤0.5	≤0.5	100.0	0.0	0.0
A. baumannii group (167)	Colistin	≤1	≤1	99.4	–	0.6
	Fosfomycin	128	128	–	–	–
	Ciprofloxacin	0.25	≥16	79.0	–	21.0
	Ceftazidime	4	≥64	–	–	–
	Gentamicin	1	≥32	83.2	–	16.8
	Meropenem	≤0.5	16	88.6	0.6	10.8
P. aeruginosa (540)	Colistin	≤1	≤1	100.0	–	0.0
	Fosfomycin	128	≥256	–	–	–
	Ciprofloxacin	0.25	≥16	72.8	5.2	22.0
	Ceftazidime	2	16	81.9	–	18.1
	Gentamicin	2	4	90.6	–	9.4
	Meropenem	≤0.5	16	77.2	12.0	10.7

Abbreviations: %-S, % susceptible strains; %-I, % intermediate strains; %-R, % resistant strains

Figure: Comparative distribution of colistin and fosfomycin MICs for MDR (red bars) and non-MDR (blue bars) isolates



Abbreviation: MDR, multidrug resistant; %-R, % resistant strains; Red line indicates EUCAST breakpoint.

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