Multidrug-resistance in *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* and susceptibility to four last-resort antimicrobials, Germany

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PURPOSE / OBJECTIVES

Infections due to multidrug-resistant (MDR) Gram-negative organisms like *Escherichia coli* (EC), *Klebsiella pneumoniae* (KP) and *Pseudomonas aeruginosa* (PA) are threatening public healthcare (1). The following MDR phenotypes have been selected as indicators to monitor antimicrobial resistance in humans: third-generation cephalosporin-resistant EC (3GCREC), third-generation cephalosporin-resistant KP (3GCRKP), carbapenem-resistant EC (CREC), carbapenem-resistant KP (CRKP), multidrug-resistant PA (MDRPA) and carbapenem-resistant PA (CRPA) (2).

We aimed to determine i) the dissemination of these MDR phenotypes among the three species, and ii) the susceptibilities to last-resort antimicrobials ceftazidime/avibactam (CTV), ceftolozane/tazobactam (CTT), imipenem/relebactam (IMR) and colistin (COL).

MATERIAL & METHODS

298 EC, 268 KP and 294 PA collected in 10 laboratories across Germany in 2018 were examined. Isolates were recovered from hospitalized patients (27% ICU patients) with respiratory tract infections (26%), followed by urinary tract infections (23%), bloodstream infections (21%), and intra-abdominal infections (20%).

Susceptibility testing was performed with the microdilution method according to ISO 20776-1 (3). EUCAST breakpoints (v.11.0) were applied (4). 3GC resistance in EC and KP was defined as resistance to ceftazidime and/or ceftriaxone. MDR in PA was defined as combined resistance to three or more antimicrobials/antimicrobial groups among piperacillin/tazobactam, ceftazidime, aminoglycosides (tobramycin), fluoroquinolones (ciprofloxacin and/or levofloxacin), and carbapenems (imipenem and/or meropenem). Genetic and phenotypic testing of carbapenemases was performed at the German National Reference Centre for Multidrug-Resistant Gram-negative Bacteria (5).

RESULTS (revised analysis)

Overall, susceptibility rates to CTV, CTT, IMR and COL were 95-100%, except for PA to COL (92%). 16.8% (50/298) of the EC and 23.5% (63/268) of the KP were resistant to 3GC. 13.9% (38/294) of the PA were MDR. CR was seen in 21.8% (64/294) of PA, 1.9% (5/268) of KP, and lacking in EC. Susceptibility rates of MDR phenotypes to CTV, CTT, IMR and COL were 76-100%, except for CRKP (**Table 1**). Overall, 6.8% (59/860) isolates were resistant to one or more last-resort antimicrobials. (**Table 2**). Two KP and one PA were resistant to CTV, CTT, IMR and COL. Susceptibility of COL-resistant isolates (n=35) was 91.4% to both CTV and IMR, and 88.6% to CTT. Carbapenemases were detected in 4/5 (80%) CRKP and 3/64 (4.7%) CRPA (**Table 3**).

SUMMARY / CONCLUSIONS

Susceptibility rates of EC, KP and PA MDR phenotypes to CTV, CTT, IMR and COL were 76-100%, except for CRKP.

Cross-resistance between COL and any of the three β-lactam / β-lactamase combinations was observed in <1% (4/860) of the isolates.

The results of the study underline the importance of CTV, CTT, IMR and COL as last-resort antimicrobials for treatment of infections due to Gram-negative organisms in patients with limited treatment options.

TABLE 1: Susceptibility of *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolates to last-resort antimicrobials[§]

Species	Resistance phenotype[§]	n	Number (%) susceptible			
			CTV	CTT	IMR	COL
E. coli	–	298	298 (100)	298 (100)	298 (100)	296 (99.3)
	3GCREC	50	50 (100)	50 (100)	50 (100)	50 (100)
K. pneumoniae	–	268	266 (99.3)	256 (95.5)	265 (98.9)	258 (96.3)
	3GCRKP	63	61 (96.8)	51 (81.0)	60 (95.2)	55 (87.3)
	CRKP	5	3 (60)	0 (0)	2 (40)	3 (60)
P. aeruginosa	–	294	286 (97.3)	283 (96.3)	285 (96.9)	271 (92.2)
	MDRPA	38	31 (81.6)	30 (78.9)	29 (76.3)	37 (97.4)
	CRPA	64	58 (90.6)	57 (89.1)	55 (85.9)	61 (95.3)

[§] 3GCREC, third-generation cephalosporin-resistant *E. coli*; 3GCRKP, third-generation cephalosporin-resistant *K. pneumoniae*; CRKP, carbapenem-resistant *K. pneumoniae*; MDRPA, multidrug-resistant *P. aeruginosa*; CRPA, carbapenem-resistant *P. aeruginosa*; [§] CTV, ceftazidime/avibactam; CTT, ceftolozane/tazobactam; IMR, imipenem/relebactam; COL, colistin

TABLE 3: Minimal inhibitory concentrations (mg/L) of carbapenemase-producing *Klebsiella pneumoniae* (n=4) and *Pseudomonas aeruginosa* (n=3) to four last-resort antimicrobials[§]

Species	Clinical isolate	CTV	CTT	IMR	COL	carbapenemase(s)
K. pneumoniae	3-39	1 (S)	>64 (R)	4 (R)	0.5 (S)	OXA-232
	5-40	>64 (R)	>64 (R)	>32 (R)	4 (R)	NDM-1, OXA-48
	5-45	>64 (R)	>64 (R)	8 (R)	16 (R)	NDM-1, OXA-181
	7-6	0.12 (S)	>64 (R)	0.25 (S)	1 (S)	KPC-3
P. aeruginosa	6-45	32 (R)	>64 (R)	>32 (R)	2 (S)	VIM-2
	13-15	32 (R)	>64 (R)	>32 (R)	2 (S)	VIM-2
	16-57	16 (R)	>64 (R)	>32 (R)	4 (R)	VIM-2

[§] CTV, ceftazidime/avibactam; CTT, ceftolozane/tazobactam; IMR, imipenem/relebactam; COL, colistin; S, susceptible; R, resistant

TABLE 2: Resistance patterns of *Escherichia coli* (n=298), *Klebsiella pneumoniae* (n=268) and *Pseudomonas aeruginosa* (n=294) isolates as regards to four last-resort antimicrobials[§]

Species	MDR phenotype[§]	Resistant to				n	%
E. coli	yes	--	--	--	COL	2	0.7
K. pneumoniae	yes	--	CTT	--	--	9	3.4
	yes	--	--	--	COL	8	3.0
	yes	--	CTT	IMR	--	1	0.4
	yes	CTV	CTT	IMR	COL	2	0.7
P. aeruginosa	yes	CTV	--	--	--	1	0,3
	yes	--	CTT			3	1.0
	yes	--	--	IMR	--	3	1.0
	no	--	--	--	COL	21	7.1
	yes	CTV	CTT	--	--	2	0.7
	yes	CTV	--	IMR	--	1	0.3
	yes	--	CTT	IMR	--	1	0.3
	no	--	CTT	--	COL	1	0.3
	yes	CTV	CTT	IMR	--	3	1.0
	yes	CTV	CTT	IMR	COL	1	0.3

[§] MDR phenotypes: third-generation cephalosporin-resistant *E. coli*, third-generation cephalosporin-resistant *K. pneumoniae*, carbapenem-resistant *K. pneumoniae*, multidrug-resistant *P. aeruginosa*, carbapenem-resistant *P. aeruginosa*; [§] CTV, ceftazidime/avibactam; CTT, ceftolozane/tazobactam; IMR, imipenem/relebactam; COL, colistin

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