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Short Communication

Is meropenem MIC increase against KPC-producing *Klebsiella pneumoniae* correlated with increased resistance rates against other antimicrobials with Gram-negative activity?

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ABSTRACT

Objectives: The aim of this study was to assess the minimum inhibitory concentration (MIC) distribution for meropenem and other antimicrobials with Gram-negative activity against *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp) clinical isolates collected at a tertiary hospital in Italy between 2013–2016.

Methods: The antimicrobial susceptibility of KPC-Kp strains was tested by the broth microdilution method using customised 96-well plates and the results were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.

Results: Among 169 consecutive KPC-Kp clinical isolates, 45 (26.6%) were susceptible to meropenem (MIC ≤ 2 mg/L). Among the 124 meropenem-resistant isolates, 73 (58.9%) had a meropenem MIC between 16–64 mg/L. The overall resistance rate for the other antimicrobials tested was very high both for ciprofloxacin and levofloxacin (99.0%), was moderate for amikacin (37.4%) and was low for gentamicin (11.2%), colistin (8.2%) and tigecycline (7.7%). Aminoglycosides had a dichotomous behaviour in relation to meropenem MIC increase. The resistance rate for gentamicin remained <20% across all meropenem MICs; conversely, that for amikacin increased from <20% in the presence of meropenem MIC ≤ 8 mg/L up to ca. 80% in the presence of meropenem MIC ≥ 64 mg/L. Resistance rates for tigecycline and colistin remained <20% in the presence of meropenem MICs up to 64 mg/L.

Conclusion: The overall susceptibility rates of antimicrobials with Gram-negative activity may vary greatly among KPC-Kp clinical isolates. A tight relationship between meropenem MIC increase and the resistance rate for amikacin was documented.

1. Introduction

The spread of *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) is a major public-health concern in many parts of the world, including Italy where it is raised to endemic proportions nowadays [1]. Although no definitive therapeutic approach against KPC-Kp infections has been established, treatment with high-dose prolonged-infusion meropenem, in combination with other active anti-Gram-negative antibacterials, appears to be helpful when dealing with KPC-Kp isolates with a meropenem minimum inhibitory concentration (MIC) of <16 mg/L [2,3].

More recently, we showed that treatment with high-dose continuous-infusion meropenem optimised by means of real-time therapeutic drug monitoring (TDM) may represent a valuable tool in improving clinical outcome even when dealing with infections caused by KPC-Kp with meropenem MICs of 32–64 mg/L [4]. Specifically, maintenance of meropenem steady-state concentrations (C_{ss}) above the MIC for the entire dosing interval (up to a maximum of 100 mg/L) was significantly associated by univariate analysis with successful clinical outcome [C_{ss}/MIC ratio ≥1: odds ratio (OR) = 10.556, 95% confidence interval (CI) 1.612–69.122;

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$P = 0.014$; C_{ss}/MIC ratio ≥4: OR = 12.250, 95% CI 1.268–118.361; $P = 0.030$] [5].

Subsequent population pharmacokinetic/pharmacodynamic (PK/PD) analysis showed that this strategy may be reliable in clinical settings with a high proportion (≥70%) of KPC-Kp clinical isolates with a meropenem MIC ≤ 32 mg/L and with a low proportion (≤10%) of isolates with an MIC > 64 mg/L [5]. Consistently, knowledge of the meropenem MIC distribution up to 64 mg/L may be pivotal in defining whether or not clinicians should consider including meropenem in the treatment of KPC-Kp infections.

The purpose of this study was to assess the meropenem MIC distribution and the susceptibility to other antimicrobials with Gram-negative activity against KPC-Kp clinical isolates collected at our hospital in 2013–2016. In addition, it was tested whether meropenem MIC increase against KPC-Kp may be correlated with resistance rates against those antimicrobials with Gram-negative activity that are used for the management of KPC-Kp infections.

2. Methods

This study retrospectively assessed the MIC distribution for meropenem and the susceptibility to antimicrobials with Gram-negative activity against KPC-Kp clinical isolates collected at a tertiary hospital in Italy between 2013–2016. Phenotypic screening and confirmation of carbapenemase production was performed according to current guidelines [6].

Antimicrobial susceptibility of the KPC-Kp strains was tested by the broth microdilution method using Sensititre™ (TREK Diagnostic Systems; Thermo Scientific, Cleveland, OH; distributed in Italy by Biomedical Service) and the results were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. Since the EUCAST breakpoint system did not reach a definite position on how to interpret the intermediate category [7], for the purpose of this study strains with intermediate susceptibility were considered as resistant.

Since 2012 at our hospital, Sensititre™ susceptibility plates for testing antimicrobials against multidrug-resistant (MDR) Gram-negative pathogens (Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) are customised as shown in Table 1. For several antimicrobials, mainly β-lactams, MIC ranges have been extended far above the EUCAST clinical breakpoints. The intent was that of knowing whether resistance associated with MDR Gram-negative bacteria may be overcome by means of PK/PD optimisation of exposure to antimicrobials with Gram-negative activity, as suggested by Cohen [8].

In the present study, the MIC distribution of KPC-Kp strains for meropenem (from 0.5 mg/L to 64 mg/L) was analysed in relation to the frequency of resistance rates only of those antimicrobials with Gram-negative activity that are usually suggested for combination with meropenem in the treatment of KPC-Kp infections, namely fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (amikacin and gentamicin), colistin and tigecycline [2,9]. Plates were incubated for 24 h in a Sensititre™ ARIS™ incubator set at 35–37 °C. Software for automatic reading of antimicrobial susceptibility was set to interpretive criteria based on EUCAST guidelines.

3. Results

A total of 169 consecutive KPC-Kp clinical isolates were isolated from urine (64/169; 37.9%), blood (43/169; 25.4%), respiratory tract (14/169; 8.3%), skin and soft-tissue bioptic samples (12/169; 7.1%), bile (7/169; 4.1%) and rectal swabs (29/169; 17.2%).

Overall, 45 (26.6%) of the KPC-Kp clinical isolates were susceptible to meropenem (MIC ≤ 2 mg/L). Among the meropenem-resistant KPC-Kp isolates (73.4%; 124/169), 26.6% (33/124) had an MIC of 4–8 mg/L, 58.9% (73/124) had an MIC between 16–64 mg/L and only 14.5% (18/124) had an MIC > 64 mg/L. Regarding the other antimicrobials with Gram-negative activity, the overall resistance rate was very high both for ciprofloxacin and levofloxacin (99.0%), was moderate for amikacin (37.4%) and was quite low for gentamicin (11.2%), colistin (8.2%) and tigecycline (7.7%).

Fig. 1 depicts the MIC distribution frequencies for meropenem for KPC-Kp clinical isolates in relation to the proportion of resistance rate against the other antimicrobials with Gram-negative activity. Resistance rates for ciprofloxacin and levofloxacin were always very high (>80%) irrespective of the meropenem MIC. Regarding the aminoglycosides, amikacin and gentamicin had

Table 1
Sensititre™ broth microdilution 96-well plate customised for antimicrobial susceptibility testing, and minimum inhibitory concentration (MIC) distribution of antimicrobials against multidrug-resistant Gram-negative isolates. Tested MICs (mg/L) for each antimicrobial are reported within the wells.

	1	2	3	4	5	6	7	8	9	10	11	12
A	TZP	TZP	TZP	TZP	TZP	TZP	TZP	COL	COL	COL	COL	COL
	128/4	64/4	32/4	16/4	8/4	4/4	2/4	8	4	2	1	0.5
B	CTX	CTX	CTX	CTX	CTX	CTX	CTX	DOR	DOR	DOR	DOR	DOR
	4	2	1	0.5	0.25	0.12	0.06	8	4	2	1	0.5
C	CIP	CIP	CIP	CIP	CIP	CIP	FEP	FEP	FEP	FEP	FEP	FEP
	2	1	0.5	0.25	0.12	0.06	32	16	8	4	2	1
D	TGC	TGC	TGC	TGC	TGC	TGC	SXT	SXT	SXT	SXT	NIT	NIT
	4	2	1	0.5	0.25	0.12	4/76	2/38	1/19	0.5/9.5	64	32
E	AMK	AMK	AMK	LVX	LVX	LVX	AMC	AMC	AMC	SAM	SAM	SAM
	16	8	4	4	2	1	8/2	4/2	2/2	32/16	16/8	8/4
F	IPM	IPM	IPM	IPM	IPM	GEN	GEN	GEN	FOS[a]	FOS[a]	FOS[a]	ETP
	16	8	4	2	1	4	2	1	64	32	16	1
G	CAZ	CAZ	CAZ	CAZ	CAZ	CAZ	CAZ	CAZ	CAZ	CAZ	CAZ	CON
	128	64	32	16	8	4	2	1	0.5	0.25	0.12	
H	MEM	MEM	MEM	MEM	MEM	MEM	MEM	MEM	MEM	MEM	CON	CON
	64	32	16	8	4	2	1	0.5	0.25	0.12		

TZP, piperacillin/tazobactam; COL, colistin; CTX, cefotaxime; DOR, doripenem; CIP, ciprofloxacin; FEP, cefepime; TGC, tigecycline; SXT, trimethoprim/sulfamethoxazole; NIT, nitrofurantoin; AMK, amikacin; LVX, levofloxacin; AMC, amoxicillin/clavulanic acid; SAM, ampicillin/sulbactam; IPM, imipenem; GEN, gentamicin; FOS, fosfomycin; ETP, ertapenem; CAZ, ceftazidime; CON, control; MEM, meropenem; EUCAST, European Committee on Antimicrobial Susceptibility Testing.
EUCAST clinical breakpoints for the Enterobacteriaceae (susceptible/resistant expressed in mg/L): AMC, ≤8/>8; SAM, ≤8/>8; AMK, ≤8/>16; FEP, ≤1/>4; CTX, ≤1/>2; CIP, ≤0.5/>1; COL, ≤2/>2; CAZ, ≤1/>4; DOR, ≤1/>4; ETP, ≤0.5/>1; FOS, ≤32/>32; GEN, ≤2/>4; IPM, ≤2/>8; LVX, ≤1/>2; MEM, ≤2/>8; NIT, ≤64/>64; TZP, ≤8/>16; SXT, ≤2/>4; TGC, ≤1/>2.
[a] Data for FOS were not presented since susceptibility was not determined by the agar dilution method as recommended by EUCAST.