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ORIGINAL ARTICLE

Empirical monotherapy with meropenem or combination therapy: the microbiological point of view

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Abstract The increase in the number of clinical isolates of multiresistant Enterobacteriaceae and *Pseudomonas aeruginosa* raises problems in decision-making on empirical treatments for severe Gram-negative bacilli-associated infections. The aim of our study is to determine the resistance of meropenem in our setting and the co-resistance of a combination of this compound with two antibiotics from different families: amikacin and ciprofloxacin. Between 2009 and 2013, a total of 81,310 clinical isolates belonging to the main species of Enterobacteriaceae and 39,191 clinical isolates of *P. aeruginosa* isolated in 28 hospitals in the Valencian Community on the South East Mediterranean Coast of Spain were analyzed using data provided by RedMiva (microbiological surveillance network of the Valencian Community). Meropenem resistance in Enterobacteriaceae increased from 0.16 % in 2009 to 1.25 % in 2013. Very few Enterobacteriaceae strains resistant to meropenem were sensitive to ciprofloxacin; in contrast, the combination of meropenem and amikacin led to a marked decrease in the risk of the microorganisms being resistant to both drugs (RR = 34 in 2013). In the case of *P. aeruginosa*, meropenem resistance also increased (from 14.32 % in 2009 to 24.52 % in 2013). Most meropenem-resistant *P. aeruginosa* isolates were also resistant to fluoroquinolones. However, the addition of amikacin led to a more than three-fold decrease in the risk of resistance. In our setting, empirical treatment with meropenem is adequate in enterobacterial infections, but poses difficulties when infection due to *P. aeruginosa* is suspected, in which case a combination of meropenem and amikacin has been shown to have a higher microbiological success rate.

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Introduction

Inadequate empirical antimicrobial treatment of serious infections has been directly linked to mortality, in particular in bacteremia, where mortalities of 30–35 % have been reported in the literature [1]. Although the concept of unsuitability includes different factors such as the dose used, the route of drug administration and duration, the most important factor is the lack of sensitivity of the organism to the antibiotic. When designing empirical treatment protocols it is therefore essential to understand the local epidemiology and evolution of antibiotic resistance in the different microorganisms [2]

The increasing number of clinical isolates of Enterobacteriaceae carriers of broad-spectrum beta-lactamases and carbapenemases and of carbapenem-resistant *Pseudomonas aeruginosa* is one of the main causes of inadequate empirical antibiotic treatment, both in bacteremia and in other serious infections. The aim of our study is, therefore, to analyze the situation of meropenem resistance in Enterobacteriaceae and *P. aeruginosa* in our area, and to study the co-resistance to a

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combination of this compound with ciprofloxacin or amikacin.

Materials and methods

A retrospective study (2009–2013) of antibiotic resistance of the most prevalent Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., and *Proteus* spp.) and *P. aeruginosa* (one isolate per patient) was carried out.

Data on the antibiotic resistance in the Valencian Community (VC) was collected from the RedMiva (microbiological surveillance network of the VC). This network collects data automatically on a daily basis (all the studies on antibiotic sensitivity carried out at each hospital) and analyzes information from 28 microbiology laboratories covering more than 90 % of the population of the region. The quality control of the process was ensured by means of a system of alerts, supervised by a group of microbiologists [3]. The VC, located in the southeast of Spain, has a population of approximately 5 million people. The antibiotic resistance data at the national and European levels were obtained from the EARS reports for the years 2009–2013 [4]. A clinical isolate is considered co-resistant to an antibiotic combination if it is resistant to or exhibits intermediate resistance to both compounds studied.

For analysis of the data for each group of microorganisms (Enterobacteriaceae and *P. aeruginosa*), percentages of resistance to meropenem (risk of resistance) were estimated for each year, according to the type of antimicrobial resistance: single meropenem resistance versus combined resistance (meropenem plus ciprofloxacin or meropenem plus amikacin). As the impact measure, risk differences (RD) with their 95 % confidence intervals (95%CI) were estimated. As measures of association, risk ratios (RR) with their 95%CI were estimated. The combined resistance was treated as the reference category. The level of statistical significance was set at 0.05 and all tests were two-tailed. All analyses were performed using SPSS v.21.0 and Epidat 3.1.

Results

A total of 81,310 clinical isolates of Enterobacteriaceae and 39,191 clinical isolates of *P. aeruginosa* were studied.

Resistance to third-generation cephalosporins in Enterobacteriaceae increased from 9.39 to 14.43 % during the study period (Table 1). In the most prevalent species, *Escherichia coli*, the average resistance in the VC, Spain, and Europe was quite similar, but for the second most prevalent species, *Klebsiella* spp., it was lower in the VC than in Spain and much lower than in Europe (Table 1).

Table 1 Resistance to third-generation cephalosporins in enterobacteria, in *E. coli*, in *Klebsiella pneumoniae*, and to meropenem in *P. aeruginosa*

	VC	Spain	Europe
Resistance (%) to third-generation cephalosporins in enterobacteria			
2009	9.39	NA	NA
2010	11.42	NA	NA
2011	12.61	NA	NA
2012	13.91	NA	NA
2013	14.43	NA	NA
Resistance (%) to third-generation cephalosporins in *E. coli*			
2009	9.41	11.3	7.9
2010	11.26	12.1	9.5
2011	12.49	12.0	9.6
2013	13.65	13.3	12.6
Resistance (%) to third-generation cephalosporins in *Klebsiella pneumoniae*			
2009	6.8	11.1	21.4
2010	8.15	10.2	22.8
2011	8.69	13.4	24.2
2012	10.1	16.7	25.6
2013	11.7	19.8	30.0
Resistance (%) to meropenem in *P. aeruginosa*			
2009	14.32	16.1	17.2
2010	13.22	17.8	17.0
2011	12.96	16.3	16.9
2012	14.95	16.4	17.1
2013	2013	17.6	17.6

VC Valencian Community, *NA* not available

Resistance to meropenem in Enterobacteriaceae was less frequent, although a progressive increase in resistance was observed during the study period (from 0.16 % in 2009 to 1.25 % in 2013). The risks of resistance for each year according to type of meropenem resistance (single versus combined resistance) are shown in Table 2.

Very few meropenem-resistant Enterobacteriaceae strains were sensitive to ciprofloxacin; thus the risk ratio increased (1.5 versus 1.8). In contrast, the combination of meropenem and amikacin led to a marked decrease in the risk of the microorganism being resistant to both compounds (RR = 34 in 2013), although clinically the difference in risk was small (RD = 1.3 %; 95 % CI 1.03–1.55).

Figure 1a shows the evolution of resistance during the years studied. There was a marked increase in resistance to meropenem and co-resistance to meropenem–ciprofloxacin, whereas co-resistance to the amikacin–meropenem combination remained stable or even declined slightly over the last few years.

As for *P. aeruginosa*, resistance to meropenem in the VC progressively increased from 14.32 % in 2009 to 24.52 % in 2013. Comparing these data with those published in the

Table 2 Risks of resistance according to type of meropenem use (single versus combined therapy with ciprofloxacin or amikacin) for Enterobacteriaceae. Valencian Community (years 2009–2013)

Year	Type of meropenem use	Resistant (*n*)	Nonresistant (*n*)	Risk of resistance (%)	RD	95 %	CI	RR	95 %	CI	*P*
2009	CIP + MEM	32	25,143	0.13	0	–	–	1	–	–	
	Only MEM	42	25,133	0.17	0.04 %	−0.03	1.1	1.31	0.83	2.08	0.245
2010	CIP + MEM	13	19,108	0.07	0	–	–	1	–	–	
	Only MEM	23	19,098	0.12	0.05 %	−0.01	0.11	1.8	0.90	3.49	0.095
2011	CIP + MEM	31	16,708	0.19	0	–	–	1	–	–	
	Only MEM	42	16,697	0.25	0.07 %	−0.03	0.16	1.35	0.85	2.15	0.197
2012	CIP + MEM	37	11,037	0.33	0	–	–	1	–	–	
	Only MEM	42	11,032	0.34	0.05 %	−0.11	0.20	1.14	0.73	1.76	0.573
2013	CIP + MEM	77	9,124	0.84	0	–	–	1	–	–	
	Only MEM	107	9,094	1.16	0.33 %	0.04	0.61	1.39	1.04	1.86	0.026
2009	AMK + MEM	14	23,067	0.06	0	–	–	1	–	–	
	Only MEM	36	23,045	0.16	0.10 %	0.03	0.15	2.57	1.39	4.77	0.002
2010	AMK + MEM	3	17,578	0.02	0	–	–	1	–	–	
	Only MEM	20	17,561	0.11	0.10 %	0.04	0.15	6.7	1.98	22.43	< 0.001
2011	AMK + MEM	15	15,358	0.10	0	–	–	1	–	–	
	Only MEM	37	15,336	0.24	0.14 %	0.05	0.23	2.47	1.35	4.49	0.002
2012	AMK + MEM	3	9,868	0.03	0	–	–	1	–	–	
	Only MEM	35	9,836	0.35	0.3 %	0.20	0.45	11.67	3.59	37.92	< 0.001
2013	AMK + MEM	3	7,675	0.04	0	–	–	1	–	–	
	Only MEM	102	7,576	1.33	1.3 %	1.03	1.55	34	10.79	107.13	< 0.001

RD risk difference, *RR* relative risk, *95%CI* 95 % confidence interval, *MEM* meropenem, *CIP* ciprofloxacin, *AMK* amikacin

European Antimicrobial Resistance Surveillance Study (EARSS) for the same period, it can be seen that at the beginning of the study period the resistance in the VC was lower than the average resistance in Spain and Europe; however, in 2013, it increased at an alarming rate and overtook both the national and the European resistance rates (Table 1).

Table 3 shows the risk of resistance for each year according to type of meropenem resistance for *P. aeruginosa*.

As in the case of Enterobacteriaceae, most of the meropenem-resistant *P. aeruginosa* strains were also resistant to fluoroquinolones, so again, the RR was of no clinical relevance (RR < 1.5 for all the years studied) with a RD of 3.7 % for the year 2013 (95%CI 2.6–4.8). However, the addition of amikacin led to a more than three-fold decrease in the risk of resistance for all the years studied, with an RD of 19.2 % for the year 2013 (95%CI 18.0–20.3)

Figure 1b shows the evolution of resistance in *P. aeruginosa* throughout the study period. Regarding the increase in meropenem resistance and in the co-resistance to meropenem and ciprofloxacin run in parallel, although there is a smaller increase in the co-resistance to amikacin and meropenem throughout the study period.

Discussion

The suitability of empirical treatment is one of the most important parameters to evaluate in patients with severe

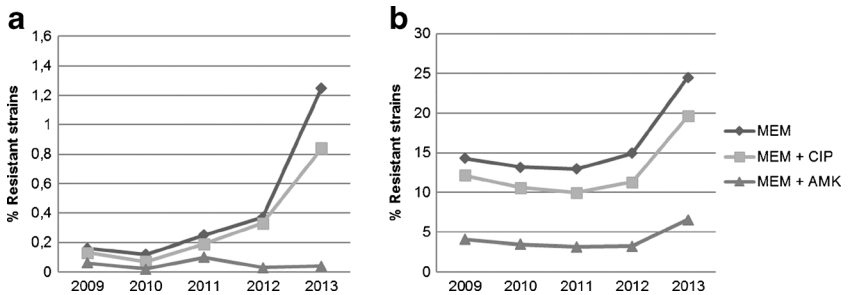

Fig. 1 Evolution of resistance according to type of meropenem use (single versus combined therapy with ciprofloxacin or amikacin). Valencian Community (years 2009–2013). **a** Enterobacteriaceae. **b** *P. aeruginosa*

Table 3 Risks of resistance according to type of meropenem use (single versus combined therapy with ciprofloxacin or amikacin) for *P. aeruginosa*. Valencian Community (years 2009–2013)

Year	Type of meropenem use	Resistant (*n*)	Nonresistant (*n*)	Risk of resistance (%)	RD	95 %	CI	RR	95 %	CI	*P*
2009	CIP + MEM	831	6,000	12.1	0	–	–	1	–	–	
	Only MEM	1,034	5,797	15.1	2.9 %	1.8	4.1	1.24	1.14	1.35	< 0.001
2010	CIP + MEM	659	5,571	10.6	0	–	–	1	–	–	
	Only MEM	845	5,385	13.6	3.0 %	1.8	4.1	1.28	1.16	1.41	< 0.001
2011	CIP + MEM	740	6,681	10.0	0	–	–	1	–	–	
	Only MEM	970	6,451	13.1	3.1 %	2.1	4.1	1.31	1.20	1.43	< 0.001
2012	CIP + MEM	969	7,581	11.3	0	–	–	1	–	–	
	Only MEM	1,271	7,279	14.9	3.5 %	2.5	4.5	1.31	1.21	1.41	< 0.001
2013	CIP + MEM	1,992	8,167	19.6	0	–	–	1	–	–	
	Only MEM	2,369	7,790	23.3	3.7 %	2.6	4.8	1.19	1.13	1.25	< 0.001
2009	AMK + MEM	277	6,493	4.1	0	–	–	1	–	–	
	Only MEM	914	5,856	13.5	9.4 %	8.5	10.3	3.30	2.90	3.76	< 0.001
2010	AMK + MEM	219	6,125	3.4	0	–	–	1	–	–	
	Only MEM	817	5,527	12.9	9.4 %	8.5	10.4	3.73	3.23	4.13	< 0.001
2011	AMK + MEM	226	6,993	3.1	0	–	–	1	–	–	
	Only MEM	928	6,291	12.9	9.7 %	8.9	10.6	4.11	3.56	4.73	< 0.001
2012	AMK + MEM	238	7,090	3.2	0	–	–	1	–	–	
	Only MEM	1,101	6,227	15	11.8 %	10.9	12.7	4.63	4.04	5.30	< 0.001
2013	AMK + MEM	511	7,262	6.6	0	–	–	1	–	–	
	Only MEM	2,000	5,773	25.7	19.2 %	18	20.3	3.91	3.57	4.29	< 0.001

infections associated with Gram-negative bacilli as it is directly associated with their survival. This suitability refers not only to the choice of antibiotic therapy, but also to the timeliness of initiation, dosing, duration, or route of administration. When deciding on the antibiotics to be used, the local rates of resistance must be taken into account because of the geographical variability of resistance [5–7]

Our study shows that, from the microbiological point of view, the protocol for empirical treatment for severe Enterobacteriaceae infection should take into account the high proportion of strains resistant to third-generation cephalosporins in our setting; hence, patients with clinical factors associated with this resistance [8, 9] should receive meropenem monotherapy. In contrast, in our environment, meropenem-resistant strains are very uncommon; thus, excluding special circumstances, it would not be necessary to administer combination therapy with other drugs. This contrasts with the situation in other geographical areas of Europe with serious problems of multidrug resistance in *Klebsiella pneumoniae* [10–12]. Only in exceptional circumstances should the addition of a second drug be considered, in which case amikacin would be the best option.

If involvement of *P. aeruginosa* is suspected, the progressive increase in the percentage of strains resistant to carbapenems, which in 2013 rose to 24.5 %, implies that monotherapy with these compounds might be microbiologically inadequate in nearly a quarter of patients, as has been described in other geographical areas [13]. Therefore, a combination with other antimicrobials is required for proper empirical handling in severe infection. When choosing the most suitable treatment combination, account must be taken of the low effectiveness of combination therapy with ciprofloxacin due to the increase in resistance detected both in our environment and in other geographical areas [14]. In contrast, our data show that combined therapy using meropenem with amikacin is the safest, as organisms that are resistant to both antibiotics are unlikely to be found.

In addition, our study shows a significant increase in antibiotic resistance in our setting in recent years, as has happened in other regions of Spain [15], which suggests the need for measures to help to control this phenomenon [16].

On the other hand, antimicrobial overuse may lead to antimicrobial resistance, unnecessary adverse effects, and increased costs. Regardless of what is chosen as empirical therapy, once culture and susceptibility results are known, the therapy should be directed at the pathogen; thus, one of the two agents should be discontinued.

These measures should include stewardship programs to ensure the correct use of antibiotics and rapid microbiological diagnostic systems to reduce the duration of incorrect empirical treatment by quickly adjusting treatment on the basis of the microbiological data to monitor the use of broad-spectrum

antibiotics, diminish toxicity, and control the rise in antibiotic resistance [17, 18].

Our data confirm that in our location, the available therapeutic options for the management of severe Gram-negative bacilli infections are rather limited, especially if involvement of *P. aeruginosa* is suspected, when the use of combined therapies may be needed for most of the severe cases [19, 20]. However, this strategy is not free of complications; thus, well-designed randomized trials should be implemented to elucidate the effectiveness of different combination regimens, [21–23]. In addition, standardized validated systems should be developed to assess the activity of various compounds in combination to better characterize the phenomena of antagonism and synergy [24].

Compliance with ethical standards

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Conflicts of interest The authors declare that they have no conflicts of interest.

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