Infection and Drug Resistance

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ORIGINAL RESEARCH

Clinical Burden of Carbapenemase-Producing Enterobacterales in Spain: A Multicenter Retrospective Study from Five Hospitals

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Introduction: This study assessed the clinical burden of carbapenemase-producing Enterobacterales (CPE) infections according to different resistance mechanisms among Enterobacterales isolates in Spain.

Methods: This retrospective study was conducted in five Spanish hospitals from the National Mapping of Carbapenemases in Spain study. Patients were included if they were 18 years or older; had a diagnosis of complicated intraabdominal infection (cIAI), complicated urinary tract infection (cUTI), bloodstream infection (BSI), or hospital-acquired or ventilator-acquired bacterial pneumonia (HABP/VABP) between 2017 and 2018; and had a confirmed CPE isolate.

Results: In total, 118 patients were evaluable for clinical outcomes. The most common mechanism of carbapenem resistance was *Klebsiella pneumoniae* carbapenemase (KPC; n = 82, 69.5%), followed by OXA-48 (n = 27, 22.9%) and metallo-β-lactamases (MBL; n = 9, 7.6%). Overall, 75 patients (63.6%) died from any cause, including 21 deaths (28.0% of all deaths) attributable to the current infection. Clinical cure was achieved in 92 patients (78.0%) and microbiological cure in 59 (54.6%). Among the 92 patients discharged alive, 29 (31.5%) were readmitted for an infectious disease, and relapse within 30 days occurred in 10 patients (10.9%).

Discussion: Data suggest that CPE infections are associated with a high disease burden, low rates of clinical cure, and high rates of relapse and mortality in Spain. However, results should be interpreted with caution due to the limited sample size which may have restricted the precision of these estimates and gaps in minimal inhibitory concentration data availability.

Keywords: enterobacterales, antimicrobial resistance, carbapenem resistant, mortality, clinical cure, microbiological cure

Introduction

Carbapenemase-producing Enterobacterales (CPE), including *Escherichia coli* and *Klebsiella pneumoniae*, have emerged as a major public health threat with a substantial impact on healthcare-associated infections. The World Health Organization (WHO) recognizes CPE (also referred to as carbapenem-resistant Enterobacterales [CRE]) as a significant public health concern. Effective infection prevention and control (IPC) practices are essential to combat antimicrobial resistance, as described in the International Health Regulations for handling international public health threats. The WHO published global IPC guidelines that synthesize expert recommendations and current evidence to support IPC improvement at facility and national levels in both public and private healthcare sectors.[1]

https://doi.org/10.2147/IDR.S574515
Received: 24 October 2025
Accepted: 17 February 2026
Published: 27 February 2026

Enterobacterales acquire resistance to carbapenems through various mechanisms, including enzyme synthesis, efflux pumps, and porin mutations, with enzyme-mediated carbapenemases being the predominant mechanism. The most common carbapenemase groups implicated in clinical resistance are KPC-type carbapenemases (Ambler class A), metallo-β-lactamases (Ambler class B), and OXA-48-like (Ambler class D).[2] The importance of molecular characterization has been emphasized in the ECDC strategic framework for the integration of molecular and genomic typing into European surveillance and multi-country outbreak investigations 2019–2021.[3] CPE encompass heterogeneous resistance mechanisms with distinct therapeutic implications. KPC-producing isolates are typically susceptible to several recently introduced β-lactam/β-lactamase inhibitor combinations, such as meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-relebactam. In contrast, metallo-β-lactamase producers are resistant to these previous combinations but remain almost always susceptible to aztreonam-avibactam and cefiderocol. OXA-48–like enzymes present variable susceptibility patterns and frequent co-production of additional β-lactamases, with ceftazidime-avibactam being the treatment of choice. Therefore, understanding the impact of specific resistance mechanisms is essential for optimizing therapeutic strategies and improving patient prognosis.[4] In Spain, the most frequent carbapenemase group implicated in clinical resistance is OXA-48, accounting for two-thirds of the cases; however, there are notable regional differences, with KPC predominantly found in the southern and southeastern parts of Spain, while OXA-48-like is more common in other areas of the country.[5]

Addressing the public health challenge posed by CPE is crucial for countries including Spain. EURGen-Net data from 37 European countries indicated further dissemination of CPE across healthcare systems in Europe between 2015 and 2018, with 11 countries reporting expansion.[6] To date, no published study in the Spanish population has specifically described the clinical burden associated with CPE or examined how resistance mechanism influences clinical outcomes. This study aimed to assess the clinical burden of CPE infections according to resistance mechanism among Enterobacterales isolates in Spain.

Materials and Methods

Study Design and Center Selection

This retrospective study was conducted in five Spanish hospitals participating in the National Mapping of Carbapenemases in Spain (CARBA-MAP) study; Hospital Universitario Reina Sofía (Córdoba, Spain), Hospital Ramón y Cajal (Madrid, Spain), Hospital Puerta del Mar (Cádiz, Spain), Hospital de Jerez de la Frontera (Jerez de la Frontera, Spain) and Hospital Clínico San Carlos (Madrid, Spain). The CARBA-MAP study was a retrospective multicenter investigation across 30 hospitals describing the first isolate per patient and year of carbapenemase-producing *E. coli, K. pneumoniae, E. cloacae complex, or K. (E). aerogenes* from clinical samples with an infection diagnosis among hospitalized patients.[5] Further details of the CARBA-MAP study are reported elsewhere.[5] The five hospitals were selected among all the sites from the CARBA-MAP study based on their relative contribution of CPE isolates (approximately 40 expected cases) from adults with complicated intraabdominal infection (cIAI), complicated urinary tract infection (cUTI), bloodstream infection (BSI), or hospital-acquired or ventilator-acquired bacterial pneumonia (HABP/VABP) infection.

The study complies with the Declaration of Helsinki principles. The study protocol was approved by the Ethics Committee of the Hospital Universitario Reina Sofía (Code 5363; Córdoba, Spain). The requirement for informed consent was waived by the Ethics Committee. No patient-identifying information was recorded in case report forms.

Selection of Patients

Patients were eligible if they were aged 18 years or older; had a diagnosis of cIAI, cUTI, BSI, or HABP/VABP between 2017 and 2018; had a confirmed CPE isolate (*E. coli, K. pneumoniae, E. cloacae, or K. [Enterobacter] aerogenes*); had at least 3 months of medical records available prior to the index infection; and had 6 months of follow-up data or had died since the infection and confirmation of the CPE isolate, whichever occurred first. Patients were excluded if isolates were obtained from surveillance samples or represented colonization rather than infection.

Data Collection and Variables

Information on patient clinical characteristics, microbiology, and outcomes was extracted from medical records. Clinical variables included demographics (age and sex), comorbidities, Charlson Comorbidity Index, type of primary infection, intensive care unit (ICU) admission including mechanical ventilation, and antibacterial treatment patterns for the index infection. Microbiological variables included type of infection and isolate identification, categorized as producing KPC-type, MBL, or OXA-48 carbapenemases. Outcomes comprised mortality (all-cause and infection-related), clinical cure (defined as cessation of antibacterial therapy or discharge for patients considered well enough to leave the hospital; the latter was based on physician judgement, resolution of signs, symptoms, or blood markers, and clinical improvement), microbiological cure (defined as having a confirmed repeated negative culture among those who achieved clinical cure), discharge, readmission, and relapse within 30 days (defined as readmission for the same infection).

Statistical Analyses

Categorical variables were presented as counts and percentages; continuous variables were presented as mean and standard deviation. Patient outcomes were stratified by resistance mechanism (OXA-48, MBL, KPC). Mortality rates, proportions of patients discharged alive, and frequencies of 30-day relapses across resistance mechanisms were compared using Fisher's exact test; $p < 0.05$ was considered statistically significant.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Overall, 128 patients were screened; 10 were excluded for not meeting selection criteria; and 118 patients were evaluable for clinical outcomes (Figure 1). The most frequently isolated CPE species was *K. pneumoniae* (n = 105, 89.0%), followed by *E. cloacae* (n = 13, 11.0%). The most common mechanism of carbapenem resistance was KPC (n = 82, 69.5%), followed by OXA-48 (n = 27, 22.9%) and MBL (n = 9, 7.6%).

The study cohort was predominantly male (62.7%) with a mean age of 69.8 years. Patients with KPC-producing Enterobacterales infections were older, although the difference was not statistically significant (Table 1). The most frequent primary infection was cUTI (40.7%), with similar distribution across resistance mechanisms. The distribution of comorbidities varied numerically across resistance mechanisms: tumor or solid neoplasia was more frequent in the OXA-48 group, while chronic obstructive pulmonary disease, diabetes, and congestive heart failure were more frequent among patients with KPC-producing Enterobacterales infections. However, none of these comorbidity differences reached statistical significance. Mean Charlson Comorbidity Index (CCI) scores were comparable between patients with KPC- and OXA-48-producing Enterobacterales infections.

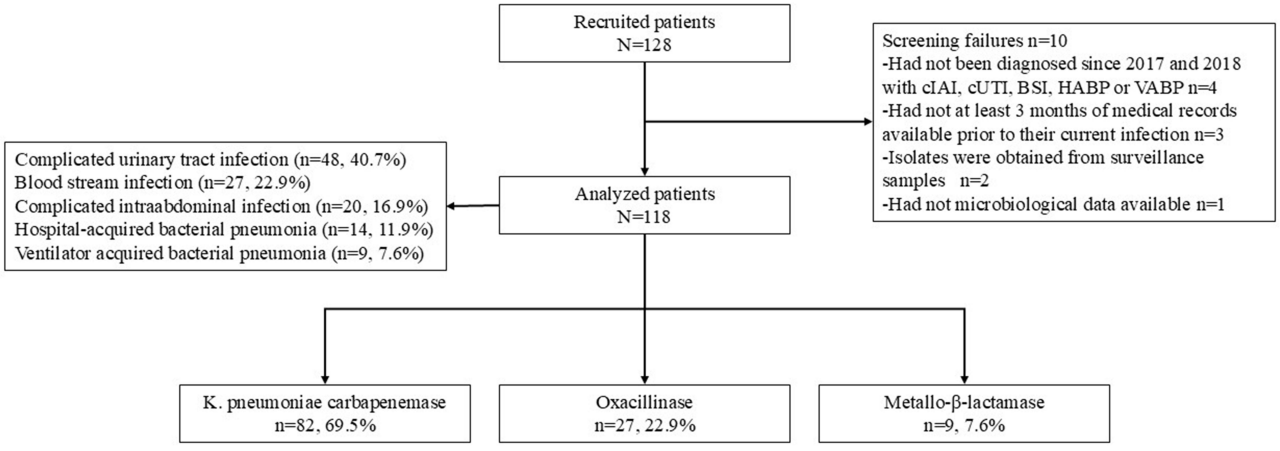

Figure 1 Patient disposition.

Abbreviations: cIAI, complicated intraabdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; N, total sample; n, absolute frequency; VABP, ventilator-acquired bacterial pneumonia.

https://doi.org/10.2147/IDR.S574515

Table 1 Patient Clinical Characteristics at Baseline

	KPC N=82		OXA-48 N=27		MBL N=9		Overall N=118		p-value**
	n*	%*	n*	%*	n*	%*	n*	%*	
Age (years), mean (SD)	71.3 (14.8)		66.4 (14.6)		66.8 (13.7)		69.8 (14.7)		0.2615
Sex (male)	50	61.0	19	70.4	5	55.6	74	62.7	0.6126
Primary infection									
Complicated urinary tract infection	34	41.5	10	37.0	4	44.4	48	40.7	0.4702†
Blood stream infection	20	24.4	5	18.5	2	22.2	27	22.9	
Complicated intraabdominal infection	14	17.1	5	18.5	1	1.2	20	16.9	
Hospital-acquired bacterial pneumonia	10	12.2	2	7.5	2	22.2	14	11.9	
Ventilator acquired bacterial pneumonia	4	4.8	5	18.5	0	0.0	9	7.6	
Charlson Comorbidity Index, mean (SD)	3.6 (2.5)		3.7 (2.6)		2.1 (1.5)		3.5 (2.5)		0.2098
Comorbidities									
Arterial hypertension	44	53.7	13	48.1	2	22.2	59	50.0	0.3707†
Tumor or solid neoplasia	24	29.3	11	40.7	3	33.3	38	32.2	0.5890
Chronic kidney disease (moderate-severe)	19	23.2	5	18.5	2	22.2	26	22.0	0.8530
Chronic obstructive pulmonary disease	20	24.4	3	11.1	1	11.1	24	20.3	0.2443
Diabetes mellitus (moderate-severe)	20	24.4	3	11.1	0	0.0	23	19.5	0.0930
Diabetes mellitus (mild)	17	20.7	6	22.2	0	0.0	23	19.5	0.2974
Dementia	18	22.0	4	14.8	0	0.0	22	18.6	0.2247
Congestive heart failure	18	22.0	1	3.7	2	22.2	21	17.8	0.0929†
Vascular disease	14	17.1	3	11.1	0	0.0	17	14.4	0.3113†
Dyslipidemia	11	13.4	6	22.2	0	0.0	17	14.4	0.2939†
Cerebrovascular disease	13	15.9	1	3.7	1	11.1	15	12.7	0.2560†
Chronic liver disease (moderate-severe)	8	9.8	5	18.5	1	11.1	14	11.9	0.6966†
Myocardial infarction	11	13.4	3	11.1	0	0.0	14	11.9	0.4791†
Intensive care admission									
ICU admission, n (%)	22	26.8	9	33.3	2	22.2	33	28.0	0.7460
LOS in the ICU, mean (SD)	18.5 (20.9)		50.2 (75.8)		4.5 (0.7)		26.3 (44.2)		0.1504
Mechanical ventilation									
Invasive mechanical ventilation									
N (%)	13	15.9	6	22.2	0	0.0	19	16.1	0.2894†
Duration (days)[b], mean (SD)	20.5 (19.3)		22.5 (21.1)		-		21.2 (19.3)		0.8495

(*Continued*)

https://doi.org/10.2147/IDR.S574515

Table 1 (Continued).

	KPC N=82		OXA-48 N=27		MBL N=9		Overall N=118		p-value**
	n*	%*	n*	%*	n*	%*	n*	%*	
Noninvasive mechanical ventilation									
N (%)	5	6.1	1	3.7	0	0.0	6	5.1	0.6828†
Duration (days)[b], mean (SD)	4.3 (2.4)		4.0 (-)		-		4.2 (2.0)		0.9306

Notes: *All data are n and % except otherwise indicated. **Comparisons were made using Fisher's exact test for categorical outcomes and ANOVA for interval outcomes. †These p-values are not accurate because the frequency of more than 25% of the cells was less than 5.
Abbreviations: ICU, intensive care unit; KPC, *Klebsiella pneumoniae* carbapenemase; LOS, length of stay; MBL, metallo-β-lactamases; N, total sample; n, absolute frequency; OXA-48, oxacillinase-48; SD, standard deviation.

Regarding hospital course, 33 (28.0%) patients required ICU admission, and 19 (16.1%) required invasive mechanical ventilation (Table 1). The most frequently prescribed empirical antibiotics were piperacillin-tazobactam (n = 29, 24.5%) and meropenem (n = 22, 18.6%), with no differences across resistance mechanism subgroups (Supplementary Table 1). The most common targeted antibiotic was ceftazidime-avibactam (n = 40, 33.9%); targeted antibiotic use differed by mechanism, with ceftazidime-avibactam most often used for KPC-producing Enterobacterales and meropenem most often used for OXA-48-producing Enterobacterales (Supplementary Table 2).

Overall, 75 (63.6%) patients died from any cause. All-cause mortality tended to be higher among patients with KPC-producing Enterobacterales infections (68.3%) than among those with OXA-48- (55.6%) or MBL-producing (44.4%) infections; however, differences were not statistically significant (p = 0.2277) (Table 2). When analyzed by cause of death, the current infection was considered responsible for death in 21 (28.0%) patients. Infection-related deaths were more common among patients with KPC-producing Enterobacterales infection (18 (32.1%) of 56 deaths) than among patients with OXA-48-producing Enterobacterales infection (3 (20.0%) of 15 deaths), but differences were not statistically significant (p = 0.2853).

The proportion of patients who achieved clinical or microbiological cure was lower among those with KPC-producing Enterobacterales infections, although differences did not reach statistical significance for clinical cure (p = 0.0995) or microbiological cure (p = 0.5212) (Figure 2). This pattern was observed across primary infection types (Supplementary Table 3). Overall, 92 (78.0%) patients were discharged alive. Discharge rates were lower among patients with KPC-

Table 2 Mortality by Resistance Mechanism and Primary Infection

	Overall		KPC		OXA-48		MBL		p-value*
	n	%	n	%	n	%	n	%	
cUTI, n (%)	32	66.7	23	67.6	7	70.0	2	50.0	0.7540**
BSI	22	81.5	16	80.0	4	80.0	2	100.0	0.7823**
cIAI	8	40.0	7	50.0	1	20.0	0	0.0	0.3529**
HABP	9	64.3	8	80.0	1	50.0	0	0.0	0.0883**
VABP	4	44.4	2	50.0	2	40.0	0	0.0	0.7642**
Overall	75	63.6	56	68.3	15	55.6	4	44.4	0.2277

Notes: *Fisher's exact test. **These p-values are not accurate because the frequency of more than 25% of the cells was less than 5.
Abbreviations: BSI, blood stream infection; cIAI, complicated intraabdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; n, absolute frequency; OXA-48, oxacillinase-48; VABP, ventilator acquired bacterial pneumonia.

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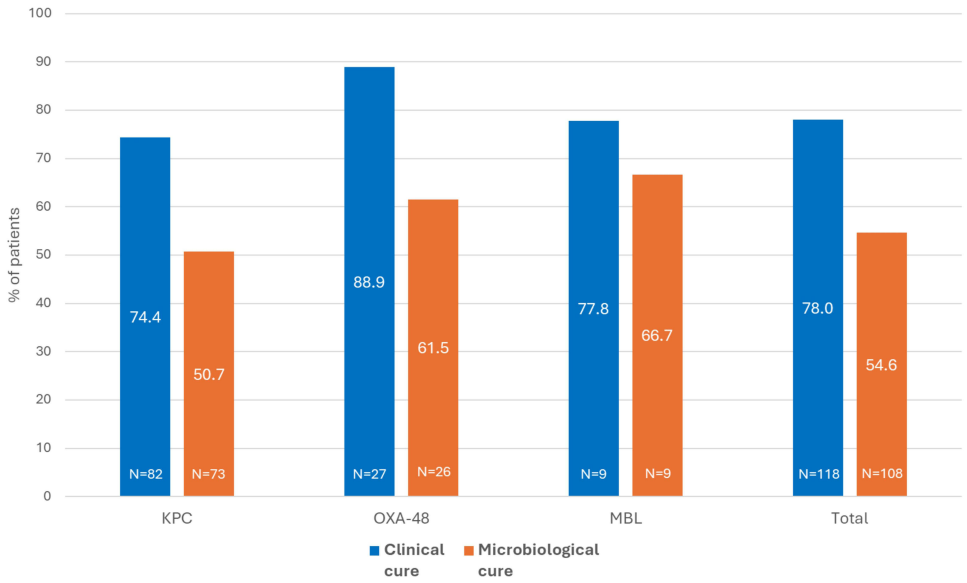

Figure 2 Clinical and microbiological cure based on mechanism of resistance. Clinical cure: this outcome was undetermined in 5, 0 and 2 patients for KPC, OXA-48 and MBL, respectively. Microbiological cure: this outcome was determined in all patients. p=0.0995 for clinical cure and p=0.5212 for microbiological cure (Fisher's exact test).
Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases; N, total sample; OXA-48, oxacillinases-48.

producing Enterobacterales infections (75.6%) compared with OXA-48- (81.5%) or MBL-producing (88.9%) infections, though differences were not statistically significant (p = 0.5815) (Table 3). Approximately one-third of discharged patients were readmitted for an infectious disease, with similar proportions in the KPC and OXA-48 groups (p = 0.2099) (Figure 3).

Relapse within 30 days occurred in 10 (10.9%) of the 92 discharged patients. Relapse was numerically higher in the OXA-48 group (4 of 22 [18.2%] discharged patients) than in the KPC group (6 of 62 [9.7%] discharged patients); no relapses were observed in the MBL group (p = 0.4730).

Table 3 Discharge by Resistance Mechanism and Primary Infection

	Overall		KPC		OXA-48		MBL		p-value*
	n	%	n	%	n	%	n	%	
cUTI, n (%)	41	85.4	29	85.3	8	80.0	4	100.0	0.6316**
BSI	17	63.0	12	60.0	4	80.0	1	50.0	0.6565**
cIAI	17	85.0	11	78.6	5	100.0	1	100.0	0.4694**
HABP	11	78.6	7	70.0	2	100.0	2	100.0	0.4660**
VABP	6	66.7	3	75.0	3	60.0	0	0.0	0.6353**
Overall	92	78.0	62	75.6	22	81.5	8	88.9	0.5815

Notes: *Fisher's exact test. **These p-values are not accurate because the frequency of more than 25% of the cells was less than 5.
Abbreviations: BSI, blood stream infection; cIAI, complicated intraabdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; n, absolute frequency; OXA-48, oxacillinase-48; VABP, ventilator-acquired bacterial pneumonia.

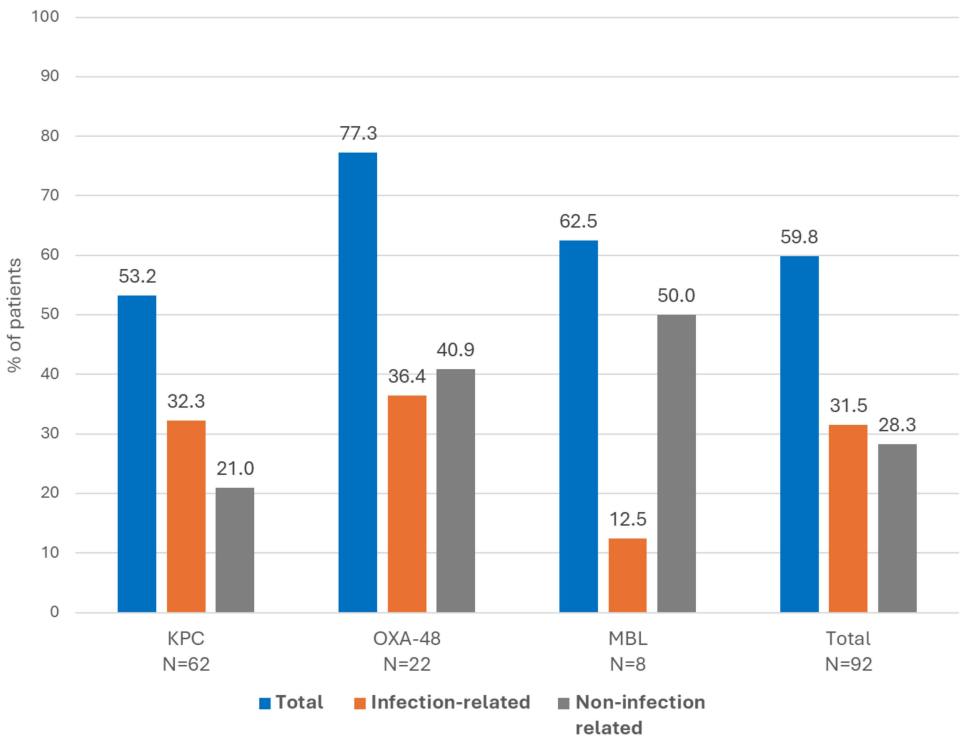

Figure 3 Readmissions based on mechanism of resistance. p=0.1001 for the overall rate of admission and p=0.2099 for the rate of infection-related admissions (Fisher's exact test).
Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases; N, total sample; OXA-48, oxacillinases-48.

Discussion

The results indicate that CPE infections in hospitalized adult patients are associated with low clinical cure rates and high rates of relapse and all-cause mortality. These findings reinforce the characterization of CPE infections as severe clinical conditions associated with substantial morbidity, mortality, and healthcare resource utilization, as previously reported in European and international cohorts.[7] Despite the widely reported increase in OXA-48–producing Enterobacterales, substantial regional variability persists. In southern and southeastern Spain, KPC has consistently been reported as the predominant carbapenemase.[5,8] Accordingly, more than two-thirds of patients in this study were recruited from three hospitals in southern Spain, and KPC was the most frequently detected carbapenemase.

Over one-fourth of patients required ICU admission, which is somewhat lower than rates reported in two UK studies (37–47%).[9,10] Nevertheless, ICU utilization remained substantial and reflects the high severity of illness associated with CPE infections, consistent with previous European studies reporting frequent ICU admission and prolonged hospital stays among patients with carbapenem-resistant Gram-negative infections.[11] Patients with OXA-48-producing Enterobacterales infections had a slightly higher frequency of ICU admission than those with KPC-producing Enterobacterales infection.

All-cause mortality in this cohort was high (63.6%), exceeding pooled mortality rates reported in systematic reviews of carbapenem-resistant *K. pneumoniae* infections.[7,12] Xu et al reported a pooled mortality of 42.1% for CR *K. pneumoniae* infections, with higher mortality in Europe (50.1%).[7] Ramos-Castañeda et al reported a 41% mortality rate among patients with KPC-producing *K. pneumoniae* infections.[12] This elevated mortality in our study may reflect the advanced age of the population, the high burden of comorbidities, and the inclusion of severe infection types such as bloodstream infection and hospital- or ventilator-acquired pneumonia. In the present cohort, mortality was numerically higher among KPC-producing Enterobacterales infections than among OXA-48-producing infections (68% vs 56%), despite similar CCI scores. Similar trends have been described in previous multicenter studies, particularly for bloodstream infections, in which KPC production has been associated with poorer outcomes and increased mortality risk.[12,13] In a cohort with similar comorbidities and comparable risk scores, we believe that the observed difference in mortality

https://doi.org/10.2147/IDR.S574515

may be attributable to the difficulty in treating KPC-producing strains, given their resistance profiles, which represent a true therapeutic challenge in the management of patients. In a study conducted by Cano et al,[14] a bundle of measures adopted for the management of this type of infection was evaluated, and an updated management algorithm for the empirical treatment of patients colonized with KPC-producing *Klebsiella pneumoniae* was proposed. This proportion is consistent with previous European data, where CRE infections were judged to contribute substantially to mortality.[15] These observations align with reports describing reduced treatment success and higher failure rates among patients with KPC-producing organisms, even in the era of newer β-lactam/β-lactamase inhibitor combinations.[16]

Consistent with the mortality findings, patients with KPC-producing Enterobacterales infections had lower clinical and microbiological cure rates than those with OXA-48-producing infections across primary infection types. However, relapse rates were numerically greater in the OXA-48 group than in the KPC group. The discrepancy between clinical and microbiological cure rates highlights the complexity of CPE management and suggests that microbiological eradication is not always achieved or documented in routine practice, which may contribute to relapse and subsequent readmissions. Additionally, the limited availability of microbiological data, including minimal inhibitory concentrations, precluded the assessment of antimicrobial adequacy, restricting the interpretation of outcome differences across carbapenemase types. This limitation is particularly relevant given that the activity of newer antimicrobial agents varies substantially according to the resistance mechanism, and current guidelines emphasize the importance of rapid molecular characterization to guide optimal therapy.[4]

Another limitation of this study was the sample size, which limited the ability to detect outcome differences by resistance mechanism and prevented adjustment of comparisons for potential confounders. Observed outcome differences by resistance mechanism should be interpreted cautiously as they may be due to unmeasured confounding. Although treatments were recorded, adequacy of therapy could not be verified. Moreover, the therapeutic landscape for carbapenemase-producing Enterobacterales in Spain has evolved with the introduction of newer agents, including meropenem–vaborbactam, imipenem–relebactam, and aztreonam–avibactam. Continued investigation is therefore warranted to generate robust data on resistance patterns and clinical outcomes associated with these novel antibiotic therapies.

Conclusion

CPE infections were associated with a substantial clinical burden, reflected by low clinical cure rates and high rates relapses and all-cause mortality. Although this burden may vary by underlying resistance mechanisms among Enterobacterales, the small sample size limited the ability to detect significant differences, and results should therefore be interpreted with caution. Larger, adequately powered studies are needed to confirm the impact of specific resistance mechanisms on clinical outcomes.

Abbreviations

BSI, bloodstream infection; CARBA-MAP, National Mapping of Carbapenemases in Spain; CCI, Charlson Comorbidity Index; cIAI, complicated intraabdominal infection; CPE, carbapenemase-producing Enterobacterales; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; HABP, hospital-acquired; ICU, intensive care unit; KPC, *Klebsiella pneumoniae* carbapenemase; LOS, length of stay; MBL, metallo-β-lactamases; N, total sample; n, absolute frequency; SD, standard deviation; VABP, ventilator-acquired bacterial pneumonia; WHO, World Health Organization.

Ethical Approval

The study protocol was approved by the Ethics Committee of the Hospital Universitario Reina Sofia (Code 5363; Córdoba, Spain). The requirement for informed consent was waived by the Ethics Committee. No patient-identifying information was recorded in case report forms.

Acknowledgments

We thank to Laura Fuentes, María Isabel López, Susana Vara, Juan Luis Sanz (APICES, Madrid; Spain) for their support with the study setup, coordination and project management, monitoring, and statistical analysis; and Fernando Rico-Villademoros (APICES, Madrid, Spain) for medical writing assistance.

Author Contributions

All authors are responsible for the work described in this paper. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Disclosure

Alexandre H. Watanabe, Emre Yücel, Yanbing Zhou and Ricardo M. Ponz are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Ana Moreno is employee of APICES, Madrid, Spain and reports professional fees from Merck. Fátima Galán-Sánchez has received speaker honorarium from Pfizer, bioMerieux, and Shionogi. The authors report no other conflicts of interest in this work.

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