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Original

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Activity of imipenem/relebactam against Enterobacterales and *Pseudomonas aeruginosa* in Spain. SMART 2016-2020

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ABSTRACT

Objectives. To determine susceptibility to the novel β-lactam/β-lactamase inhibitor combination imipenem/relebactam in clinical isolates recovered from intra-abdominal (IAI), urinary (UTI), respiratory (RTI) and bloodstream (BSI) infections in the SMART (Study for Monitoring Antimicrobial Resistance Trends) study in SPAIN during 2016 – 2020.

Methods. Broth microdilution MICs for imipenem/relebactam and comparators were determined by a central laboratory against isolates of Enterobacterales and *Pseudomonas aeruginosa*. MICs were interpreted using EUCAST-2021 breakpoints.

Results. In total, 5,210 Enterobacterales and 1,418 *P. aeruginosa* clinical isolates were analyzed. Imipenem/relebactam inhibited 98.8% of Enterobacterales. Distinguishing by source of infection susceptibility was 99.1% in BSI, 99.2% in IAI, 97.9% in RTI, and 99.2% in UTI. Of intensive care unit isolates (ICU) 97.4% were susceptible and of non-ICU isolates 99.2% were susceptible. In Enterobacterales, activity against Class A, Class B and Class D carbapenemases was 96.2%, 15.4% and 73.2%, respectively. In *P. aeruginosa*, imipenem/relebactam was active in 92.2% of isolates. By source of infection it was 94.8% in BSI, 92.9% in IAI, 91.7% in RTI, and 93.1% in UTI. An 88.7% of ICU isolates and 93.6% of non-ICU isolates were susceptible to imipenem/relebactam. Imipenem/relebactam remained active against *P. aeruginosa* ceftazidime-resistant (76.3%), cefepime-resistant (73.6%), imipenem-resistant (71.5%) and piperacillin-resistant (78.7%) isolates. Of all multidrug-resistant or difficult-to-treat resistance *P. aeruginosa* isolates, 75.1% and 46.2%, respectively, were susceptible to imipenem/relebactam.

Conclusions. Imipenem/relebactam showed high rates of susceptibility in Enterobacterales and *P. aeruginosa* isolates from different sources of infection as well as depending on patients' location (ICU or non-ICU scenarios).

Keywords: Imipenem/relebactam, Spain, Multidrug-resistant, Intensive Care Unit, β-lactam/β-lactamase inhibitor combination

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Actividad de imipenem/relebactam frente a Enterobacterales y *Pseudomonas aeruginosa* en España. SMART 2016-2020

Objetivos. Determinar la sensibilidad a la nueva combinación de β-lactámico e inhibidor de β-lactamasas imipenem/relebactam en aislados clínicos procedentes de infecciones intraabdominales (IIA), urinarias (ITU), respiratorias (ITR) y bacteriemias del estudio SMART (Study for Monitoring Antimicrobial Resistance Trends) en ESPAÑA durante 2016 - 2020.

Métodos. Se determinó la CMI mediante microdilución en caldo de imipenem/relebactam y antibióticos comparadores

frente a aislados de Enterobacterales y *Pseudomonas aeruginosa*. Las CMI se analizaron empleando los puntos de corte EUCAST-2021.

Resultados. En total, se incluyeron 5.210 aislados de Enterobacterales y 1.418 aislados de *P. aeruginosa*. Imipenem/relebactam fue activo frente al 98,8% de los Enterobacterales. Distinguiendo por foco de infección, la sensibilidad fue del 99,1% en bacteriemia, del 99,2% en IIA, del 97,9% en ITR y del 99,2% en ITU. El 97,4% de los aislados procedentes de unidades de cuidados intensivos (UCI) fueron sensibles, y el 99,2% de los aislados no procedentes de UCI. En Enterobacterales, la sensibilidad frente a carbapenemasas de clase A, clase B y clase D fue del 96,2%, 15,4% y 73,2%, respectivamente. En *P. aeruginosa*, imipenem/relebactam fue activo en el 92,2% de los aislados. Distinguiendo por foco de infección, la sensibilidad frente a *P. aeruginosa* fue del 94,8% en bacteriemia, 92,9% en IIA, 91,7% en ITR y 93,1% en ITU. El 88,7% de los aislados de la UCI y el 93,6% de los aislados no procedentes de UCI fueron sensibles a imipenem/relebactam. Imipenem/relebactam fue activo frente a aislados de *P. aeruginosa* resistentes a ceftazidima (76,3%), cefepima (73,6%), imipenem (71,5%) y piperacilina/tazobactam (78,7%). Frente a los aislados de *P. aeruginosa* clasificados como MDR o DTR, el 75,1% y el 46,2%, respectivamente, fueron sensibles a imipenem/relebactam.

Conclusiones. Imipenem/relebactam mostró elevada sensibilidad frente a los aislados de Enterobacterales y *P. aeruginosa* procedentes de diferentes focos de infección, así como en función de la localización de los pacientes (UCI o no UCI).

Palabras clave: Imipenem/relebactam, España, multirresistencia, Unidad de Cuidados Intensivos, combinación de β-lactámico/inhibidor de β-lactamasa

INTRODUCTION

The growing global rising trend of antimicrobial resistance (AMR) represents a major healthcare problem, increasing mortality and healthcare costs [1]. A report from the Global Burden of Disease Study in 2019 estimates 4.95 and 1.27 million deaths associated and attributable to AMR, respectively [2]. These numbers will continue to increase, reaching 10 million attributable deaths by 2050 according to estimates from the UK government [3]. Extended-Spectrum β-lactamase (ESBL) and carbapenemase producing Enterobacterales (CPE) or carbapenem resistant *Pseudomonas aeruginosa* (CPPA), and multidrug-resistant (MDR) or difficult-to-treat resistance (DTR) are some of the resistance phenotypes with worrying public health implications, which severely limit treatment options [4–6]. In the past years, very few novel antimicrobials with novel mechanisms of action have been developed [7]. Consequently, combinations of already known antibiotics with specific enzyme-inhibitors are very valuable options. Imipenem/relebactam is a new β-lactam/β-lactamase inhibitor combination with broad spectrum activity against Ambler class A β-lactamases (including ESBL and KPC) and class C β-lactamases (AmpC) [8].

Susceptibility rates of imipenem/relebactam and comparators agents, including other β-lactam/β-lactamase inhibitor combinations, such as ceftazidime/avibactam and ceftolozane/tazobactam, were analysed against a collection of Enterobacterales and *P. aeruginosa* isolates recovered from intra-abdominal (IAI), urinary (UTI), respiratory (RTI) and bloodstream (BSI) infections in the SMART (Study for Monitoring Antimicrobial Resistance Trends) study in SPAIN during 2016 – 2020.

METHODS

Bacterial isolates. From 2016 to 2020, 11 Spanish hospitals collected up to 250 consecutive, clinically significant Gram-negative isolates per year. Sources of infection were blood, intra-abdominal, lower respiratory tract, and urinary tract. Only one isolate per Gram-negative species per patient per year was accepted. All isolates were shipped to a central laboratory (IHMA, Schaumburg, IL, USA) where identification of bacterial species was confirmed by MALDI-TOF (matrix-assisted laser desorption ionization-time of flight) before antimicrobial susceptibility testing was performed.

Antimicrobial susceptibility testing. Antimicrobial susceptibility was evaluated by broth microdilution at the central laboratory following the standard ISO recommendations**.** The antimicrobials tested were: amikacin, aztreonam, cefepime, ceftazidime, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, colistin, ertapenem, imipenem, imipenem/relebactam, levofloxacin, meropenem, and piperacillin/tazobactam. Antimicrobial susceptibility results were interpreted using EUCAST MIC breakpoints (version 11.0, 2021) [9]. When isolates were categorized as "I" (formerly "intermediate" and now indicating "susceptible, increased exposure"), the percentage of "I" isolates were collated with "S" isolates ("susceptible, standard dose") and presented as susceptible. Multidrug-resistant (MDR) *P. aeruginosa* and Enterobacterales were defined phenotypically as those isolates resistant to any three or more of the following eight sentinel antimicrobial agents: amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, colistin, imipenem and piperacillin/tazobactam. DTR was defined as Enterobacterales or *P. aeruginosa* isolates resistant to all of the following antimicrobials: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem, ciprofloxacin and levofloxacin.

Molecular characterization. Molecular testing criteria included all Enterobacterales isolates, excluding *Serratia* spp., with an imipenem or imipenem/relebactam MIC ≥2 mg/mL or a ceftolozane/tazobactam MIC ≥4 mg/mL. In *P. aeruginosa*, isolates with an imipenem or imipenem/relebactam MIC ≥4 mg/mL or a ceftolozane/tazobactam MIC ≥8 mg/mL. Molecular testing consisted on screening for β-lactamase genes encoding the metallo-β-lactamases (IMP, VIM, NDM, GIM, and SPM), serine carbapenemases [KPC, GES, and OXA-48-like (Enterobacterales) or OXA-24-like (*P. aeruginosa*)], ESBLs (SHV, TEM, CTX-M, VEB, PER, and GES), acquired AmpC β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, MOX), and the AmpC sequence variations [*Pseudomonas*-derived cephalosporinase (PDC) variants] using published multiplex PCR assays, followed by full-gene DNA se-

quencing [10]. For *Serratia* spp., only isolates with imipenem MIC >4 mg/mL (resistant) or imipenem/relebactam MIC >2 mg/mL were screened for β-lactamase genes.

RESULTS

In total, 5,210 Enterobacterales and 1,418 *P. aeruginosa* clinical isolates were included. Distribution of species included by source of infection is detailed in Figure 1a. Globally, 37.8% of isolates were from RTI, 27.7% from IAI, 23.2% from UTI and 11.2% from BSI. MDR isolates in Enterobacterales ranged from 3.4% in *Serratia marcescens* to 28.9% in *Klebsiella aerogenes*. In *P. aeruginosa*, MDR accounted for 29.2%. Frequency of DTR isolates in Enterobacterales was low (≤1.0%) in every species, whereas 2.8% of *P. aeruginosa* isolates were DTR (Figure 1b). Differentiating the isolates from patients admitted in the Intensive Care Units (ICU), with respect to those who were not (non-ICU), MDR and DTR frequencies were higher in ICU for both Enterobacterales and *P. aeruginosa* (Figure 1c). Frequency of carbapenemase-production was as follows: *E. cloacae* (7.2%), *E. coli* (0.4%), *K. aerogenes* (1.0%), *K. pneumoniae* (12.1%), *S. marcescens* (1.7%) and *P. aeruginosa* (2.8%).

Imipenem/relebactam overall activity against Enterobacterales was 98.8%, and, distinguishing by source of infection it was 99.1% in BSI, 99.2% in IAI, 97.9% in RTI, and 99.2% in UTI. Ceftazidime/avibactam and meropenem displayed the highest susceptibility rates (≥99.0%). Table 1 shows the antimicrobial susceptibility data by species. Imipenem/relebactam was active in more than 96.4% in every single Enterobacterales species. Against CPE, imipenem/relebactam was active against 96.2% of Class A, 15.4% of Class B and 73.2% of Class D carbapenemases. With regard to the activity of other β-lactam/β-lactamase inhibitor combinations against CPE, in this study, ceftazidime/avibactam showed 100% susceptibility against Class A and Class D. Table 2 shows the susceptibility to imipenem/relebactam in ICU and non-ICU isolates as well as against MDR and DTR phenotypes. Among Enterobacterales, 97.4% of ICU isolates and 99.2% of non-ICU isolates were susceptible to imipenem/relebactam. In CPE, imipenem/relebactam was active in 59.7% and 73.2% of ICU or non-ICU isolates, respectively. However, considering only Class A CPE isolates, activity was 100% and 95.2% in ICU and non-ICU respectively. Against MDR Enterobacterales, imipenem/relebactam was active in 85.7% of ICU and 94.3% of non-ICU isolates. Activity of at least 88.9% was retained in MDR isolates resistant to 3 to 5 (out of 8) sentinel antimicrobial agents in both ICU and non-ICU scenarios. Against DTR Enterobacterales, imipenem/relebactam was only susceptible in 16.7% of non-ICU isolates.

Regarding *P. aeruginosa* the most potent agents tested were colistin (99.4%) and amikacin (94.5%). The activity of imipenem/relebactam was 92.2%, similar to ceftolozane/tazobactam (92.8%) and ceftazidime/avibactam (92.3%). Activity of imipenem/relebactam by source of infection was 94.8% in bacteraemia, 92.9% in IAI, 91.7% in RTI, and 93.1% in UTI. Imipenem/relebactam remained active against *P. aeruginosa* isolates resistant to different β-lactams, such as ceftazidime-resistant (76.3%), cefepime-resistant (73.6%), imipenem-resistant (71.5%) and piperacillin-resistant (78.7%). Of all MDR isolates, 75.1% were susceptible to imipenem/relebactam, similar to ceftolozane/tazobactam (76.3%), and higher than ceftazidime/avibactam (73.6%). Against DTR isolates, imipenem/relebactam showed 46.2% susceptibility, which was better than all other β-lactam/β-lactamase inhibitor combinations. Imipenem/relebactam was not active against carbapenemase-producers (Table 1). Among *P. aeruginosa*, 88.7% of ICU isolates and 93.6% of non-ICU isolates were susceptible to imipenem/relebactam. With respect to MDR *P. aeruginosa*, imipenem/relebactam was active in 70.6% of ICU and 77.8% of non-ICU isolates. Activity of at least 81.4% was retained in MDR isolates resistant to 3 to 4 (out of 8) sentinel antimicrobial agents in both ICU and non-ICU scenarios. Against DTR *P. aeruginosa*, imipenem/relebactam was susceptible in 38.5% and 50.0% of ICU or non-ICU isolates, respectively (Table 2).

Overall, 173 (2.6%) [62 (1.2%) Enterobacterales and 111 (7.8%) *P. aeruginosa*)] isolates were resistant to imipenem/relebactam. Resistant isolates were as follows: *E. coli* (*n*=1; VIM-1), *K. pneumoniae* [*n*=43, OXA-48 (32), VIM-1 (6), NDM-1 (4), KPC-3 (1)], *E. cloacae* [*n*=11, VIM-1 (8), OXA-48 (3)], *K. aerogenes* (*n*=2, NDM-1, one isolate not characterized), *S. marcescens* [n=5, OXA-48 (2), VIM-1 (2), one isolate not characterized] and *P. aeruginosa* [*n*=111, VIM-1 (11), VIM-2 (10), VIM-20 (7), GES-5 (7), IMP-13 (2), IMP-like (2), PER-1 (1), *Pseudomonas*-derived cephalosporinases only, PDCs (62), nine isolates not characterized]. Details of molecular characterization of resistant isolates are shown in Supplementary table 1.

DISCUSSION

Global burden of AMR is increasing worldwide causing 1.27 million attributable deaths in 2019 [2]. In addition, antibiotic consumption is continuously growing, as shown by a recent report illustrating an increase of 46% between 2000 and 2018 [11]. Nevertheless, the development of new antibiotics is not enough to mitigate the situation. Efforts should focus on innovating and developing new antimicrobials or alternative therapies, along with surveillance studies to monitor the AMR trends.

Here we present the results of the SMART surveillance study in Spain, focused on the activity of imipenem/relebactam. In this report, we have considered only the resistant isolates for MDR and DTR classifications, using the new EUCAST definitions in which susceptible isolates combine "S" category with "I" (susceptible, increased exposure) category. In other publications, the non-susceptible isolates (intermediate + resistant) are included together [12,13]. Such a difference causes variations in the total number of isolates belonging to MDR/DTR categories and in the rates of susceptibility. As an example, in this dataset, DTR isolates only represent 0.3% in Enterobacterales and 2.8% in *P. aeruginosa*. If we had considered non-susceptible isolates together (intermediate + resistant), DTR would represent 1.3% in Enterobacterales and 26.3% in *P. aeruginosa*.

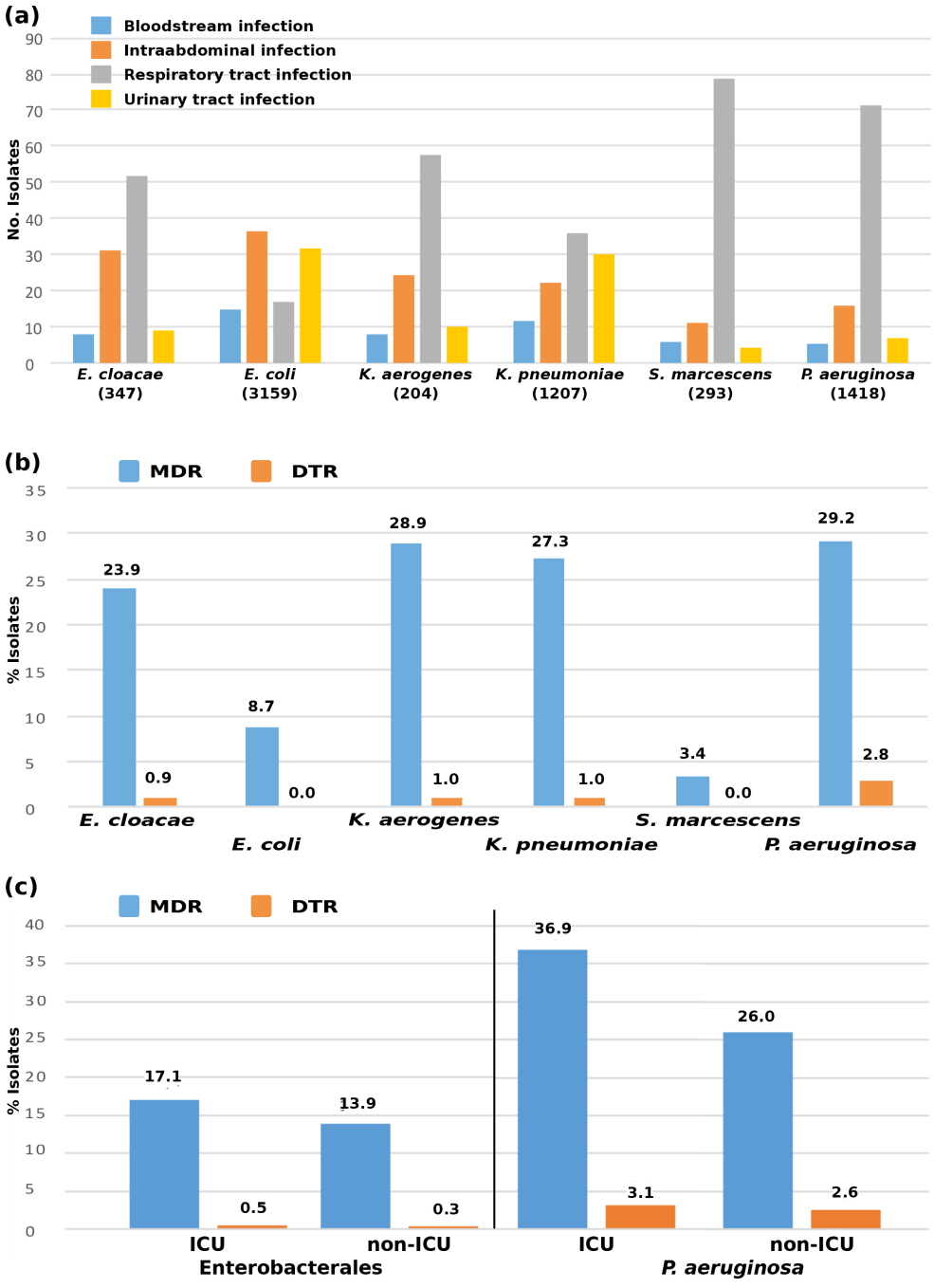

Figure 1 Distribution of species and MDR/DTR frequencies included in the study: a) Distribution of species included by source of infection. b) Frequencies of MDR and DTR isolates by species. c) Frequencies of MDR and DTR in ICU or non-ICU scenarios.

MDR, multidrug-resistant; DTR, difficult-to-treat resistance; ICU, intensive care unit

In this study, imipenem/relebactam showed high activity against Enterobacterales, with susceptibility rates of 97.4% in ICU and 99.2% in non-ICU scenarios. Furthermore, it inhibited ≥97.9% of Enterobacterales regardless of infection type. These results are in agreement with previous SMART reports in Europe, that showed 98.4% and 98.5% activity in isolates from IAI and UTI [14]. Imipenem/relebactam also retains activity against Class A (96.2%) carbapenemases, which is slightly lower than a pre-

Table 1 **Antimicrobial susceptibility of imipenem/relebactam and comparator agents against Enterobacterales and *P. aeruginosa* collected in Spain from 2016 – 2020.**

Microorganism (n)	TZP	CAZ	FEP	ATM	C/T	CZA	IPM	IPR	MEM	ETP	CIP	LVX	AMK	CST
Enterobacterales (5,210)	82.7	84.7	88.1	84.3	93.9	99.5	98.7	98.1	99.2	95.1	70.5	73.0	98.1	92.6
E. coli (3,159)	89.2	90.6	92.1	89.3	99.0	100	100	99.9	99.9	99.3	67.7	68.7	98.4	99.5
K. pneumoniae (1,207)	68.2	72.0	73.0	72.6	85.4	99.4	96.4	96.4	97.3	86.5	65.0	71.4	97.1	95.0
E. cloacae (347)	73.8	73.8	89.3	76.1	80.7	96.1	96.8	96.8	97.7	84.7	86.3	86.2	99.1	90.5
K. aerogenes (204)	65.2	68.1	98.0	71.1	81.9	100	97.6	99.0	99.0	94.1	91.3	95.1	98.5	99.0
S. marcescens (293)	94.2	97.6	98.3	98.3	97.3	100	97.3	98.3	99.3	98.3	91.8	94.5	97.6	-
CPE (190)[a]	1.6	14.7	14.2	18.4	12.1	82.7	69.5	68.4	78.4	4.2	10.2	14.7	86.3	78.4
Class A (26)	7.7	3.9	7.7	0.0	3.9	100	19.2	96.2	57.7	7.7	0.0	0.0	73.1	84.6
Class B (26)	0.0	0.0	0.0	42.3	0.0	12.5	30.8	15.4	50.0	11.5	6.7	23.1	65.4	80.8
Class D (138)	0.7	19.6	18.1	17.4	15.9	100	86.2	73.2	87.7	2.2	11.4	15.9	92.8	76.8
P. aeruginosa (1,418)	68.9	72.6	74.3	80.2	92.8	92.3	73.6	92.2	87.8	-	63.6	57.4	94.5	99.4
CAZ-resistant (388)	9.3	0.0	79.9	45.4	75.0	72.3	36.9	76.3	65.7	-	37.2	27.1	85.8	99.0
FEP-resistant (364)	9.9	14.8	0.0	40.9	73.1	68.6	36.3	73.6	61.5	-	31.6	22.0	83.5	98.9
IMP-resistant (375)	28.3	34.7	38.1	55.5	78.1	79.2	0.0	71.5	56.5	-	24.7	17.1	85.9	98.9
PTZ-resistant (441)	0.0	20.2	25.6	43.1	79.1	76.7	39.0	78.7	70.0	-	36.8	24.5	88.0	99.1
MDR (414)	6.5	15.5	17.2	38.2	76.3	73.6	30.7	75.1	61.6	-	29.2	19.1	85.0	99.0
DTR (39)	0.0	0.0	0.0	0.0	41.0	37.5	0.0	46.2	0.0	-	0.0	0.0	82.1	100
CPPA (39)[b]	10.3	0.0	5.1	74.4	2.6	35.0	0.0	0.0	2.6	-	2.0	0.0	41.0	100

TZP, piperacillin-tazobactam; CAZ, ceftazidime; FEP, cefepime; ATM, aztreonam; C/T, ceftolozane/tazobactam; CZA, ceftazidime-avibactam; IPM, imipenem; IPR, imipenem/relebactam; MEM, meropenem; ETP, ertapenem; CIP, ciprofloxacine; LVX, levofloxacine; AMK, amikacine; CST, colistine; CPE, Carbapenemase-producing Enterobacterales; MDR, multidrug-resistant; DTR, difficult-to-treat resistance; CPPA, Carbapenemase-producing *P. aeruginosa*.

[a]Carbapenemase-producing *Enterobacterales* (CPE) included the following species and types: *E. coli* n=12 [OXA-48 (8); KPC-3 (2); KPC-type, (1); VIM-1, (1)]; *K. pneumoniae* n=146 [OXA-48 (111); OXA-244 (1); KPC-3 (21); KPC-2 (1); NDM-1 (5); VIM-1, (7)]; *E. cloacae* n=25 [OXA-48 (15); GES-6 (1); VIM-1 (9)]; *K. aerogenes* n=2 [NDM-1 (1); OXA-48 (1)]; *S. marcescens* n=5 [OXA-48 (2); VIM-1 (3)]

- **Class A: KPC-3 (23), KPC-2 (1), KPC-type (1), GES-6 (1)**
- **Class B: VIM-1 (20), NDM-5 (6)**
- **Class D: OXA-48 (137), OXA-244 (1)**

[b]Carbapenemase-producing P. aeruginosa (CPPA) included the following types: VIM-1 (11), VIM-2 (10), VIM-20 (7), IMP-13 (2), IMP-like (2), GES-5 (7)

vious Spanish surveillance report, where 100% activity was observed [15]. Regarding MDR phenotypes, imipenem/relebactam inhibited 85.7% and 94.3% of Enterobacterales of ICU and non-ICU, respectively, similar to previous reports where MDR Enterobacterales showed an activity between 93.9% – 98.1% [14,16].

Against *P. aeruginosa*, imipenem/relebactam inhibited 92.2% of isolates, a slightly lower rate than a previous Spanish multicentre study in 2017, in which 97.3% of clinical isolates where susceptible [17]. Analysing by infection type, imipenem/relebactam showed that ≥91.7% of *P. aeruginosa* isolates were susceptible. Similar results were reported in isolates from IAI (94.4%) or UTI (93.0%) in Europe [14]. Relebactam restored imipenem susceptibility in 71.5% and 75.1% of *P. aeruginosa* imipenem-resistant and MDR isolates, respectively; similar to a previous SMART study in the United States [16]. Regarding activity in ICU, imipenem/relebactam inhibited 88.7% of *P. aeruginosa*, less than non-ICU isolates (93.6%), which is partly justified by a higher rate of MDR in the ICU scenario. Imipenem/relebactam did not show activity against CPPA. Those isolates carried GES-5 or different metallo-β-lactamases, against which it does not exhibit activity [14].

While in imipenem/relebactam-resistant Enterobacterales isolates, all were CPE, in *P. aeruginosa*; only 35.1% of imipenem/relebactam-resistant isolates were CPPA. Nevertheless, without using a whole genome sequencing analysis, it is not possible to correctly characterize other implicated resistance mechanisms, especially in *P. aeruginosa*, such as mutations in the porin OprD [18,19].

Among limitations of this study included that carbapenemase production was only evaluated among isolates non-susceptible to imipenem or imipenem/relebactam or ceftolozane/tazobactam.

Table 2 **Antimicrobial susceptibility of imipenem and imipenem/relebactam against Enterobacterales and *P. aeruginosa* including MDR phenotypes in ICU and non-ICU scenarios**

	ICU		non-ICU	
Microorganism (n, ICU/n non-ICU)	IPM	IPR	IPM	IPR
Enterobacterales (1,067/4,143)	97.4	97.4	99.0	99.2
E. coli (430/2,729)	100	100	100	99.9
K. pneumoniae (299/908)	96.3	93.6	96.4	97.4
E. cloacae (124/223)	94.4	96.0	98.2	97.3
K. aerogenes (89/115)	94.4	97.8	100	100
S. marcescens (125/168)	96.0	98.4	100	98.2
CPE (67/123)	71.6	59.7	68.3	73.2
Class A (5/21)	28.6	100	19.0	95.2
Class B (14/12)	28.6	14.3	33.3	16.7
Class D (48/90)	89.6	68.8	84.4	75.6
MDR total (182/574)	86.3	85.7	93.2	94.3
MDR 3* (59/189)	100	96.6	100	99.5
MDR 4 (28/179)	82.1	89.2	98.9	98.9
MDR 5 (63/155)	88.9	88.9	93.5	95.5
MDR 6 (26/39)	69.2	65.4	56.4	61.5
MDR 7 (5/12)	20.0	20.0	25.0	33.3
MDR 8 (1/0)	0.0	0.0	-	-
DTR (5/12)	0.0	0.0	0.0	16.7
P. aeruginosa (415/1,003)	63.1	88.7	77.9	93.6
CAZ-resistant (139/249)	29.5	71.9	41.0	78.7
FEP-resistant (133/231)	31.6	69.9	39.0	75.8
IMP-resistant (153/222)	-	71.2	-	71.6
PTZ-resistant (163/278)	33.7	72.4	42.1	82.4
MDR total (153/261)[a]	26.1	70.6	33.3	77.8
MDR 3 (23/55)	43.5	82.6	49.1	94.5
MDR 4 (46/70)	50.0	89.1	57.1	81.4
MDR 5 (59/80)	11.9	64.4	21.3	75.0
MDR 6 (23/47)	0.0	39.1	4.3	63.8
MDR 7 (2/7)	0.0	50.0	14.3	28.6
MDR 8 (0/2)	0.0	-	0.0	-
DTR (13/26)	0.0	38.5	0.0	50.0
CPPA (15/24)	0.0	0.0	0.0	0.0

ICU, intensive care unit; IPM, imipenem; IPR, imipenem/relebactam; CPE, Carbapenemase-producing *Enterobacterales*; MDR, multidrug-resistant; DTR, difficult-to-treat resistance; CPPA, Carbapenemase-producing *P. aeruginosa*.

[a]MDR nº, resistant to 3/4/5/6/7 or 8 of the eight sentinel antimicrobial agents

In conclusion, imipenem/relebactam showed high rates of susceptibility in Enterobacterales and *P. aeruginosa* isolates from different sources of infection as well as depending on patients' location (ICU or non-ICU scenarios). These results place imipenem/relebactam as an attractive therapeutic option to alternate with already marketed β-lactam/β-lactamase inhibitor combinations and ensure that antimicrobial stewardship is preserved.

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CONFLICTS OF INTEREST

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REFERENCES

1. Dadgostar P. Antimicrobial Resistance: Implications and Costs. Infect Drug Resist 2019;12:3903–10. doi: 10.2147/IDR.S234610
2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022 12;399:629–55. doi: 10.1016/S0140-6736(21)02724-0
3. Tackling drug-resistant infections globally : final report and recommendations / the Review on Antimicrobial Resistance chaired by Jim O'Neill. doi: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf Accessed 05 February 2023.
4. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, et al Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis. 2018;67(12):1803-1814. doi: 10.1093/cid/ciy378.
5. Livermore DM, Nicolau DP, Hopkins KL, Meunier D. Carbapenem-Resistant Enterobacterales, Carbapenem Resistant Organisms, Carbapenemase-Producing Enterobacterales, and Carbapenemase-Producing Organisms: Terminology Past its "Sell-By Date" in an Era of New Antibiotics and Regional Carbapenemase Epidemiology. Clin Infect Dis. 2020;71:1776–82. doi: 10.1093/cid/ciaa122
6. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81. doi: 10.1111/j.1469-0691.2011.03570.x
7. Talbot GH, Jezek A, Murray BE, Jones RN, Ebright RH, Nau GJ, et al. The Infectious Diseases Society of America's 10 × '20 Initiative (10 New Systemic Antibacterial Agents US Food and Drug Administration Approved by 2020): Is 20 × '20 a Possibility? Clin Infect Dis 2019;18;69:1–11. doi: 10.1093/cid/ciz089
8. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against *Enterobacteriaceae* and *Pseudomonas aeruginosa*. J Antimicrob Chemother 2013;68:2286–90. doi: 10.1093/jac/dkt178
9. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0, 2021. http://www.eucast.org.
10. Nichols WW, de Jonge BLM, Kazmierczak KM, Karlowsky JA, Sahm DF. In Vitro Susceptibility of Global Surveillance Isolates of *Pseudomonas aeruginosa* to Ceftazidime-Avibactam (INFORM 2012 to 2014). Antimicrob Agents Chemother 2016;60:4743–9. doi: 10.1128/AAC.00220-16
11. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, et al. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. Lancet Planet Health 2021;5:e893–904. doi: 10.1016/S2542-5196(21)00280-1
12. Karlowsky JA, Lob SH, Raddatz J, DePestel DD, Young K, Motyl MR, et al. In Vitro Activity of Imipenem/Relebactam and Ceftolozane/Tazobactam Against Clinical Isolates of Gram-negative Bacilli With Difficult-to-Treat Resistance and Multidrug-resistant Phenotypes-Study for Monitoring Antimicrobial Resistance Trends, United States 2015-2017. Clin Infect Dis 2021;15;72:2112–20. doi: 10.1093/cid/ciaa381
13. Torrens G, van der Schalk TE, Cortes-Lara S, Timbermont L, del Barrio-Tofiño E, Xavier BB, et al. Susceptibility profiles and resistance genomics of *Pseudomonas aeruginosa* isolates from European ICUs participating in the ASPIRE-ICU trial. J Antimicrob Chemother. 2022;29;77:1862-1872 doi: 10.1093/jac/dkac122
14. Lob SH, Karlowsky JA, Young K, Motyl MR, Hawser S, Kothari ND, et al. In vitro activity of imipenem-relebactam against resistant phenotypes of Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples – SMART Surveillance Europe 2015–2017. J Med Microbiol. 2020;69:207–217. doi: 10.1099/jmm.0.001142
15. Vázquez-Ucha JC, Seoane-Estévez A, Rodiño-Janeiro BK, González-Bardanca M, Conde-Pérez K, Martínez-Guitián M, et al. Activity of imipenem/relebactam against a Spanish nationwide collection of carbapenemase-producing Enterobacterales. J Antimicrobial Chemother. 2021;76:1498–1510. doi: 10.1093/jac/dkab043
16. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In-vitro activity of imipenem/relebactam and key βlactam agents against Gram-negative bacilli isolated from lower respiratory tract infection samples of intensive care unit patients – SMART Surveillance United States 2015–2017. Int J Antimicrob Agents. 2020;55:105841. doi: 10.1016/j.ijantimicag.2019.10.022
17. Fraile-Ribot PA, Zamorano L, Orellana R, López-Causapé C, Cabot G, Bou G, et al. Activity of Imipenem-Relebactam against a Large Collection of *Pseudomonas aeruginosa* Clinical Isolates and Isogenic B-Lactam-Resistant Mutants. Antimicrobial Agents and Chemotherapy 2020;64:6. doi: 10.1128/AAC.02165-19.
18. Gomis-Font MA, Cabot G, Sánchez-Diener I, Fraile-Ribot PA, Juan C, Moya B, et al. In vitro dynamics and mechanisms of resistance development to imipenem and imipenem/relebactam in *Pseudomonas aeruginosa*. J. Antimicrobial Chemother. 2020;75:2508–2515. doi: 10.1093/jac/dkaa206

19. Young K, Painter RE, Raghoobar SL, Hairston NN, Racine F, Wisniewski D, et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against *Pseudomonas aeruginosa.* BMC Microbiol 2019 4;19:150. doi: 10.1186/s12866-019-1522-7