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In vitro activity of cefiderocol against ESBL-producing and carbapenem-resistant *Pseudomonas aeruginosa*

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Objectives: To determine the activity of cefiderocol against 101 Peruvian *Pseudomonas aeruginosa* isolates.

Methods: Carbapenem– and/or third- and fourth-generation cephalosporin–resistant *P. aeruginosa* clinical isolates were isolated in nine Peruvian health centres. Antibiotic susceptibility was established by automated methods and/or disc diffusion (10 antimicrobial agents), colistin agar test (colistin) and microdilution (cefiderocol). The presence of bla_{PER}, $bla_{CTX\text{-}M}$, bla_{GES}, bla_{KPC}, bla_{IMI}, bla_{IMP}, bla_{NDM}, $bla_{OXA\text{-}23}$, $bla_{OXA\text{-}24}$, $bla_{OXA\text{-}48}$, $bla_{OXA\text{-}58}$, bla_{VIM} and *oprD* was established by PCR; $bla_{CTX\text{-}M}$ and *oprD* were sequenced. The levels of antimicrobial resistance ranged from 20.8% (colistin) to 97.0% (meropenem).

Results: The MIC of cefiderocol ranged from ≤0.06 to 8 mg/L (one isolate). Cefiderocol resistance rates were 1.0% (according to the FDA and EUCAST) and 0% according to CLSI, whereas 14.9% and 1.0% of isolates were classified as cefiderocol-intermediate according to FDA and CLSI, respectively. CTX-M-131 and GES, and IMP and VIM were the most frequent ESBLs and carbapenemases, respectively. The presence of *oprD* mutations was tested in 47 carbapenem-resistant isolates, 23 with *oprD*-inactivating mutations as the sole underlying mechanism. Although no specific association was found between the presence of ESBLs and carbapenemases with cefiderocol resistance, carbapenemase-producing isolates tended to present slightly higher cefiderocol MIC values. The cefiderocol-resistant isolate did not present ESBLs or carbapenemases, showing only an *oprD*-inactivating mutation.

Conclusions: Cefiderocol showed excellent activity against *P. aeruginosa*, irrespective of the presence of ESBLs and/or carbapenemases. The high number of isolates bordering cefiderocol-resistant levels suggests the need for cautious use and continuous surveillance of this antibiotic.

Introduction

The high levels of use, abuse and misuse of antibacterial agents have had a high impact on antibiotic-susceptible bacterial populations and the selection and/or development of antibiotic-resistant microorganisms, which have expanded throughout all environments and geographical areas.[1–3] In fact, antibiotic resistance is challenging current clinical practices,

severely impacting the treatment of infectious diseases and also hindering interventions, such as organ transplantation,[4] thereby threatening to return the treatment and prevention of infectious diseases to the pre-antibiotic era.

This problem has a worldwide dimension. Notwithstanding its planetary effect, the problem of antibiotic resistance is of special concern in low- and middle-income countries.[3] This finding is related to a series of sociocultural and economic factors, including over-the-counter access to antibacterials and the difficulty in accessing or the precarity of health facilities.[5,6] The magnitude of the current problem has led the WHO to consider antimicrobial resistance amongst the most critical current health challenges (https://www.who.int/news-room/photo-story/detail/urgent-health-challenges-for-the-next-decade), being considered a real risk for achieving Sustainable Development Goals.[7]

In this scenario, the development of new antibacterial agents is urgently needed. In recent years, several antibiotics have been developed and some have been introduced into the clinical practice.[8–10] Among these, cefiderocol is a new cephalosporin that is recognized by bacteria as a siderophore.[11] Thus, in addition to classical pathways of cephalosporin intake, this antibacterial agent uses a bacterial backdoor—the bacterial ion-acquisition systems—to cross bacterial barriers, acting as a true Trojan horse.[11] This results in optimal activity levels against a series of pathogenic bacteria, otherwise resistant to other antimicrobial agents, including other third- and fourth-generation cephalosporins.[11] Hence, cefiderocol is active against a series of Gram-negative microorganisms of special concern, including carbapenem-resistant *Pseudomonas aeruginosa*.[8,12–14]

P. aeruginosa is a ubiquitous microorganism, which can be recovered from a great variety of environments and sources.[2,15] This microorganism may act as an opportunistic pathogen, being a frequent cause of infections in ICUs,[2] in which the presence of *P. aeruginosa* resistant to specific antibacterial agents, such as carbapenems, has a direct impact on fatal outcomes.[16]

Peru is a middle-income country in which the current levels of antimicrobial resistance are worrisome.[17–19] Regarding *P. aeruginosa*, different reports have shown high levels of resistance to carbapenems and antipseudomonal cephalosporins.[2,20] In Peru, the aforementioned levels of carbapenem resistance are mostly related to OprD alterations,[21] with descriptions of several carbapenemases, such as those belonging to IMP or VIM families, as well as the GES family, which may act as ESBLs or carbapenemases.[22–24]

In this scenario, the present study aimed to evaluate the activity of cefiderocol against carbapenem-resistant and/or ceftazidime/cefepime-resistant clinical isolates of *P. aeruginosa* collected in different Peruvian healthcare centres.

Materials and methods

Microorganisms

A total of 101 carbapenem– and/or ceftazidime/cefepime–non-susceptible clinical isolates of *P. aeruginosa* were included in the study. The isolates were collected between 2016 and 2022 in nine different Peruvian hospitals from four Peruvian regions (Table 1), and identified through automated methods (VITEK-2; bioMérieux, Marcy l'Etoile, France).

Antimicrobial susceptibility

Antimicrobial susceptibility, except for that of colistin and cefiderocol, was established through automated methods (VITEK-2) and disc diffusion in agar.[25] The MIC of colistin was established in accordance with CLSI procedures.[25] Regarding cefiderocol, the MIC was established by microdilution in 96-well plates using iron-depleted media (RUO Iron-depleted broth, Remel, Lenexa, USA), in agreement with previously described procedures.[25,26] Briefly, as a first approach, the concentrations of cefiderocol in the ELISA plates ranged from 0.06 to 2 mg/L. An extended MIC (2 to >64 mg/L) was performed in all isolates growing in wells containing 2 mg/L of cefiderocol. In all cases, a positive (tested bacteria grown in media without cefiderocol) and blank (non-inoculated media) were used as controls. Thin growth is not considered when the MIC of cefiderocol is determined;[25–27] thus, to avoid subjective eye-read differences in the interpretation of data,[28] all plates were read in an ELISA reader (SYNERGY LX; Biotek, Santa Clara, CA, USA) at a wavelength of 600 nm, with bacterial growth being considered when the OD was >0.100, approximately 2.5 times higher than that of blank (non-inoculated culture media) absorbance values.[26] Isolates bordering the established OD breakpoint (i.e. $0.09 \leq OD \leq 0.110$) were classified as dubious and MIC testing was repeated.[26]

In all cases, results were interpreted following the CLSI guidelines.[25] In addition, cefiderocol resistance levels were also determined according to the EUCAST and FDA guidelines.[29,30] In addition to a series of randomly selected isolates in which the cefiderocol MIC was performed twice as a quality control, the cefiderocol MIC of all isolates qualifying as resistant for any of the above-mentioned guidelines was performed up to three times, for confirmation and validation. A discrepancy of one dilution was considered inherent to the methodology, and the MIC that was common in at least two assays was reported. *Escherichia coli* ATCC 25922 was used as the quality control in all assays.

ESBLs

In all isolates, the presence of bla_{PER}, bla_{GES} and $bla_{CTX\text{-}M}$ was established by PCR as described elsewhere (Table 2).[19,31] Additionally, when $bla_{CTX\text{-}M}$ was present, the group (i.e.: 1, 2, 8, 9) was established by PCR (Table 2).[19] Amplified products were gel recovered (E.Z.N.A. Gel Extraction Kit; Omega Bio Tek, Norcross, GA, USA) and sequenced (Macrogen, Seoul, South Korea) to determine the exact $bla_{CTX\text{-}M}$ gene variant.

Carbapenemases

The presence of bla_{KPC}, bla_{IMI}, bla_{IMP}, bla_{NDM}, $bla_{OXA\text{-}23}$-like, $bla_{OXA\text{-}24}$-like, $bla_{OXA\text{-}48}$-like, $bla_{OXA\text{-}58}$-like and bla_{VIM} was determined by PCR as previously described (Table 2).[31–33]

oprD gene

The presence of *oprD* gene alterations was sought in 47 isolates showing resistance or intermediate profiles to at least one carbapenem. The *oprD* gene was amplified using the following conditions: 5 min × 95°C, 30 × (1 min × 95°C, 1 min × 60°C, 1 min × 72°C), 7 min × 72°C. Amplified products were resolved in a 1.5% agarose gel stained with 5% Sybr Safe, and gel recovered and sequenced as above (Table 2).

Ethical issues

The study was approved by the Institutional Review Board of Universidad Cientifica del Sur (code: 066-2020-PRO99).

Results

In addition to third- and fourth-generation cephalosporins and carbapenems; for which values of non-susceptibility of up to 98% were determined for meropenem in agreement with the inclusion criteria; the isolates included in the study showed high

Table 1. *Pseudomonas aeruginosa* clinical isolates included in the study

No. of isolates	Centre	Region	Area	Year
3	A[a]	El Callao[b]	Metropolitan Lima	2021
15	B[a]	Lima	Metropolitan Lima	2021 (11), 2022 (4)
3	C[a]	Lima	Metropolitan Lima	2021
4	D[a]	Lima	Metropolitan Lima	2021
53	E	Lima	Metropolitan Lima	2016 (52), 2022 (1)
11	F	Lima	Metropolitan Lima	2021
2	G	Lima	Metropolitan Lima	2021
2	H[a]	Arequipa	Southern Peru	2021
4	I[a]	Piura	Northern Peru	2021
4	ND	ND	ND	2021

ND, not determined (no data about the exact geographical origin were available).
[a]Health centres belonging to the same clinical consortium.
[b]El Callao is a special administrative region in Peru, but is physically located within Metropolitan Lima.

Table 2. Primers used in the study

	Primer sequence				
Gene	Forward (5′ → 3′)	Reverse (5′ → 3′)	Size, bp	Annealing temperature, °C	Reference
bla$_{CTX-M}$-like	CGATGTGCAGTACCAGTAA	TTAGTGACCAGAATCAGCGG	585	60	19
bla$_{CTX-M-G1}$-like	GTTACAATGTGTGAGAAGCAG	CCGTTTCCGCTATTACAA	1041	50	19
bla$_{CTX-M-G2}$-like	ATGATGACTCAGAGCATTCG	TCAGAAACCGTGGGTTAC	877	52	19
bla$_{CTX-M-G8}$-like	TGATGAGACATCGCGTTAAG	TAACCGTCGGTGACGATTTT	875	52	19
bla$_{CTX-M-G9}$-like	TGACCGTATTGGGAGTTTCAG	GATTTATTCAACAAAACCAG	917	55	19
bla$_{GES}$	CTGGCAGGGATCGCTCACTC	TTCCGATCAGCCACCTCTCA	600	57	31
bla$_{PER}$	AGTGTGGGGGCCTGACGAT	GCAACCTGCGCAATRATAGCTT	725	57	31
bla$_{KPC}$	TCGCCGTCTAGTTCTGCTGTCTTG	ACAGCTCCGCCACCGTCAT	353	57	31
bla$_{NDM}$	ACTTGGCCTTGCTGTCCTT	CATTAGCCGCTGCATTGAT	603	57	31
bla$_{IMI}$	CTACGCTTTAGACACTGGC	AGGTTTCCTTTTCACGCTCA	482	57	33
bla$_{VIM}$	TGTCCGTGATGGTGATGAGT	ATTCAGCCAGATCGGCATC	437	57	31
bla$_{IMP}$	ACAYGGYTTRGTDGTKCTTG	GGTTTAAYAAARCAACCACC	387	57	31
bla$_{OXA-48}$-like	ATGCGTGTATTAGCCTTATCG	CATCCTTAACCACGCCCAAATC	265	57	31
bla$_{OXA-23}$-like	TACAAGGGATTCGGCATCG	TAATGGCCTGTTCCCATGTG	570	52	32
bla$_{OXA-24}$-like	AAAATCTGGGTACGCAAACG	ACATTATCCGCTGGAACAGG	271	52	32
bla$_{OXA-58}$-like	TCGACACACCTTGGTCTGAA	AACTTCCAACTTTGCCATGC	477	52	32
oprD	GGCAGAGATAATTTCAAAACCAA	GTTGCCTGTCGGTCGATTAC	1384	60	21

levels of antimicrobial resistance to other antipseudomonal antibacterial agents, ranging from 38.6% for piperacillin/tazobactam to 82.2% for cefepime. Additionally, a large number of isolates were classified as intermediate for different antimicrobial agents, such as piperacillin/tazobactam, with 34.7% of intermediate isolates (Table 3). Of note, resistance to colistin was 20.8% (MIC ranged from 4 to 8 mg/L), with most of the colistin-resistant isolates (14 of 21, 67%) being recovered in the same centre (Hospital E) (Tables 1 and 3). Disregarding cefiderocol, 30 isolates showed non-susceptibility to all the antimicrobial agents tested (the 'susceptible' category was not considered for colistin, which only qualifies as intermediate or resistant), including 9 isolates fully resistant to colistin, and thereby potentially pan-resistant. Of these 30 isolates, 5 presented a MIC of cefiderocol of 2 mg/L (intermediate according to the FDA, but susceptible according to the CLSI and EUCAST), and 1 had a MIC of 8 mg/L (4, 8 mg/L and 8 mg/L in the three replicate MIC assays), thereby qualifying as intermediate according to the CLSI and resistant according to the remaining criteria considered.

Regarding cefiderocol, the range of MICs varied from ≤0.06 to 8 mg/L (MIC ≤ 0.06, 4 isolates; MIC = 0.125, 6 isolates; MIC = 0.25, 20 isolates; MIC = 0.5, 33 isolates; MIC = 1, 22 isolates; MIC = 2, 15 isolates, MIC = 8, 1 isolate) with MIC_{50} and MIC_{90} of 0.5 mg/L and 2 mg/L, respectively. Only one isolate from a Lima health centre presented a MIC > 2 mg/L (MIC = 8 mg/L), which was categorized as intermediate by CLSI and resistant by EUCAST and FDA (Table 3). As mentioned above, this isolate was resistant to all the remaining antimicrobial agents tested, except colistin, which

Table 3. Antibiotic susceptibility of the 101 *Pseudomonas aeruginosa* isolates

Antibiotic	S [n (%)]	I [n (%)]	R [n (%)]
ATM	13 (12.9)	21 (20.8)	67 (66.3)
CAZ	24 (23.8)	17 (16.8)	60 (59.4)
FEP	11 (10.9)	2 (1.9)	83 (82.2)
TZP	27 (26.7)	35 (34.7)	39 (38.6)
CZA[a]	50 (49.5)	—	51 (50.5)
IPM	2 (2.0)	2 (2.0)	97 (96.0)
MEM	2 (2.0)	1(1.0)	98 (97.0)
CIP	16 (15.8)	8 (7.9)	77 (72.6)
GEN	32 (31.7)	1(1.0)	68 (67.3)
AMK	49 (48.5)	5 (4.9)	47 (46.5)
CST[a]	—	80 (79.2)	21 (20.8)
FDC (FDA)	85 (84.2)	15 (14.9)	1 (1.0)
FDC (CLSI)	100 (99.0)	1 (1.0)	0 (0.0)
FDC (EUCAST)	100 (99.0)	0 (0.0)	1 (1.0)

AMK, amikacin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; CZA, ceftazidime/avibactam; FDC, cefiderocol; FEP, cefepime; GEN, gentamicin; I, intermediate; IPM, imipenem; MEM, meropenem; R, resistant; S, susceptible; TZP, piperacillin/tazobactam.

[a]The dashes in CZA and CSP represents not established values for these categories.

was categorized as intermediate (MIC ≤0.5 mg/L). Finally, the most conservative breakpoint (that of FDA) also identified 15 *P. aeruginosa* isolates as intermediate (Table 3). Regarding *E. coli* ATCC 25922, its cefiderocol MIC ranged from 0.125 mg/L to 0.25 mg/L in the assays developed, within the considered valid interval as per CLSI rules.[24] Regarding colistin-resistant isolates, the MIC of cefiderocol ranged from ≤0.06 mg/L (one isolate) to 2 mg/L (one isolate), with 0.5 mg/L being the most common MIC (nine isolates).

The search for ESBLs showed that 23 isolates presented $bla_{\text{CTX-M-131}}$ and 1 presented $bla_{\text{CTX-M-2}}$. Additionally, 15 isolates were positive for universal CTX-M primers but no specific group was detected. It is noteworthy that all the $bla_{\text{CTX-M-131}}$-producing isolates were recovered from the same centre in Lima City (Hospital E). The presence of bla_{GES} was detected in 13 isolates. No bla_{PER} was detected. (Table 4).

Most isolates (38 of 47) presented inactivating alterations in the OprD protein, either internal STOPs or base insertions/deletions leading to frameshift mutations (Table 4). Two of nine isolates with non-inactivating alterations showed a 50 amino acid deletion, whereas another presented an inserted proline at amino acid position 70; the remaining isolates presented a series of punctual amino acid substitutions when compared with the OprD of *P. aeruginosa* PAO1. Seven of nine isolates with non-inactivating OprD alterations possessed bla_{GES} (seven isolates), concomitantly with a bla_{IMP} in one case, and bla_{NDM} (one isolate). Thus, in these isolates carbapenem resistance remained unexplained in only one case. However, 23 of 38 (60.5%) isolates with inactivating alterations at OprD did not present any of the carbapenemases or bla_{GES} sought.

The most common carbapenemase genes were bla_{VIM} and bla_{IMP}, accounting for 9 and 20 positive isolates, respectively. Meanwhile, one isolate possessed bla_{NDM}. Of note, in several cases, more than one carbapenemase was detected concomitantly in the same isolate (Table 4). No association between the presence of ESBLs, carbapenemases, OprD alterations or a combination of the above was correlated with the development of resistance to cefiderocol; the isolate showing a MIC of 8 mg/L did not possess any carbapenamase or ESBL and presented the alteration Y_{49}* in OprD. The same OprD alteration was detected in four other isolates, with the MIC of cefiderocol ranging from 0.5 mg/L to 2 mg/L. Nevertheless, the presence of carbapenemases correlated with a trend for higher levels of resistance, with the range of cefiderocol MICs being ≤0.06 to 2 mg/L when only ESBLs were detected, and being 0.25 mg/L to 2 mg/L when carbapenemase(s) were present (Table 4, Figure 1).

Discussion

P. aeruginosa is an opportunistic pathogen frequently isolated in sensitive environments, such as ICUs or burns units.[2,23] In addition to low-permeability and potent efflux pumps, this microorganism has a great facility to become resistant to antimicrobial agents by acquisition of exogenous genetic material or because of the development of chromosomal mutations.[34,35] This finding has led to the common isolation of multi-resistant *P. aeruginosa*, showing the need for new therapeutic alternatives.[34] Although this is a worldwide trend, the situation in low- and middle-income countries is dire, due to the presence of several other limitations, such as economic barriers, poor access to health facilities, or lack of adequately trained personnel, which, combined with an easy over-the-counter access to antimicrobial agents and a deficient healthcare-related culture, results in worrisome levels of antimicrobial resistance to most of the antimicrobial agents available.[5,6]

Among others, cefiderocol has been proposed for the treatment of severe pathogens, such as *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *P. aeruginosa*.[11] In the present study, the activity of cefiderocol was tested against *P. aeruginosa* exhibiting high levels of resistance to a great variety of antimicrobial agents, including colistin, with the inclusion criteria being resistance to carbapenems or antipseudomonal cephalosporins. The results showed excellent activity of cefiderocol, irrespective of the presence of carbapenemases or ESBLs, with only 1 isolate showing a MIC of 8 mg/L, and 15 exhibiting MICs of 2 mg/L. The excellent activity of cefiderocol against colistin-resistant isolates should be mentioned, with none being considered resistant according to any of the three guidelines considered, and only one qualified as intermediate by the FDA.[25,29,30] This is of special relevance considering the use of colistin as a last-resort antimicrobial agent.[36]

In agreement with the present results, previous studies have shown that the presence of VIM, IMP or NDM in *P. aeruginosa* isolates was not consistently associated with resistance to cefiderocol, with the MICs of this agent ranging from 0.06 to 4 mg/L.[8,12–14] These findings were irrespective of the concomitant presence of more than one carbapenemase, similar to what was observed by our group.[14] Nevertheless, isolates presenting carbapenemases tend to have slightly higher cefiderocol MIC levels than those not possessing carbapenemases. In this regard, of note was the high number of isolates (eight isolates) with a MIC of 2 mg/L, classified

Table 4. Main OprD alterations[a]

Frameshift			
Insertion	Deletion	STOP	Other
G_{678} (5)	C_{212} (4)	W_{277} (1)	Δ $_{335}$GEKSWQARYDLNLASYGVPGLTFMVRYINGKDIDGTKMSDNNVGYKNYGY$_{374}$ (2)[b]
G_{262} (1)	$_{285}$GCTC$_{288}$ (1)	Y_{49} (5)	:: $_{208}$CCT$_{210}$ (1)[c]
$_{714}$AA$_{715}$ (1)	T_{915} (4)	W_{417} (7)	
C_{1206} (1)	A_{887} (1)	W_{339} (1)	
G_{855} (1)	$_{1114}$AT$_{1115}$ (1)		
A_{1222} (1)	A_{710} (1)		
G_{450} (1)			
C_{678} (1)			

The numbers in parentheses are the number of isolates possessing a specific change.
[a]No alterations other than amino acid changes or well-established non-inactivating alterations (e.g. $_{372}$V-DSSSSYAGL-Y$_{384}$) were observed in the remaining six isolates.
[b]Although stated as a 'non-inactivating mutation' because neither frameshift nor premature STOP codon was present, a severe effect on OprD functionality is the most probable scenario.
[c]The insertion encodes proline.

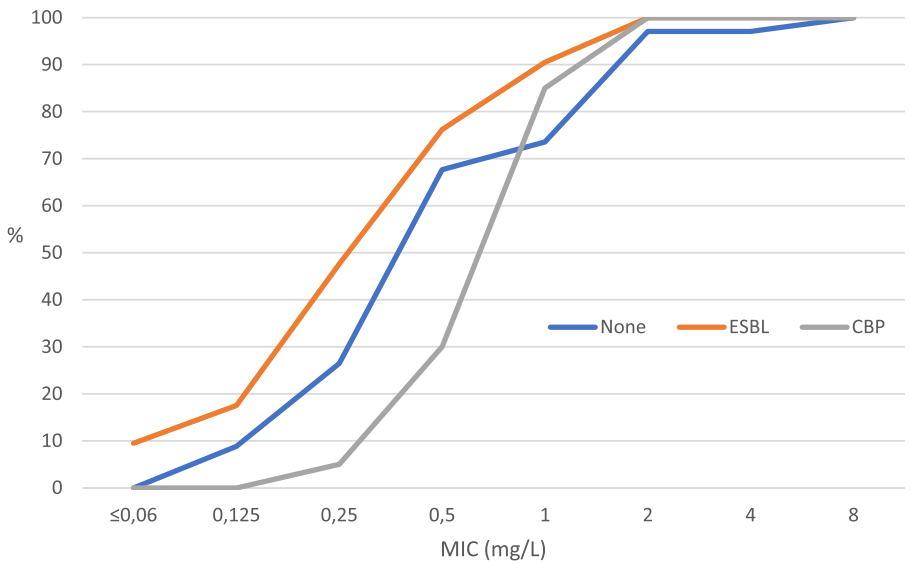

Figure 1. Cumulative cefiderocol MIC distributions. CBP, carbapenemases.

as cefiderocol intermediate according to FDA criteria and in which no mechanism of resistance sought was detected.

The only isolate with a MIC of 8 mg/L carried neither an ESBL nor carbapenemase sought and possessed only an inactivating alteration in OprD. Isolates with similar cefiderocol MIC levels, with no specific mechanisms of resistance (ESBL or carbapenemase), have also been reported in other studies.[8,12] Different aspects may underlie these MIC levels, including alterations in siderophore receptors, modifications leading to cefiderocol-inactivating PDCs (*Pseudomonas*-derived cephalosporinases), as well as the presence of unsought ESBLs or carbapenemases (studies in process).[37] In this sense, we detected a high number of isolates (eight isolates) with a MIC of 2 mg/L, classified as cefiderocol-intermediate according to FDA criteria, and in which no sought mechanism of resistance was found. Regarding the OprD amino acid substitution Y_{49}* observed in the cefiderocol-resistant isolate, its presence in other isolates, including one with a MIC of 0.5 mg/L, did not support a role in the development of resistance to cefiderocol. Furthermore, the presence of an additional great variety of OprD-inactivating mutations irrespective of cefiderocol MIC levels, precludes considering OprD inactivation as being involved in cefiderocol resistance. In agreement with our results, previous studies of the mechanisms of carbapenem resistance amongst Peruvian *P. aeruginosa* isolates have shown OprD mutations as the main contributor.[21]

In any case, the presence of cefiderocol non-susceptible isolates in the absence of the use of this agent highlights the need to preserve cefiderocol by adhering to rational and structured

use to maintain its activity as long as possible, and avoid the appearance of cefiderocol-resistant isolates.[38]

It is worth mentioning that several studies have shown the prevalence of carbapenem resistance among *P. aeruginosa* in Peruvian ICUs is up to levels of 70% or higher.[2,39] In the present study, the inclusion criteria referred only to carbapenem– and/or third- and fourth-generation cephalosporin–resistant *P. aeruginosa*. Hence, the levels of resistance to the remaining antimicrobial agents should be considered representative of the resistance to other antipseudomonal agents among these specific subpopulations of *P. aeruginosa* in the area, delineating a worrisome scenario in which near pan-resistant isolates are circulating in Peruvian health centres, thus highlighting the urgent need for new therapeutic options. In this regard, studies of the use of cefiderocol in treating life-threatening infection with no alternative treatment options, including infections by *P. aeruginosa*, have shown 28 day survival rates higher than 75%.[14] This scenario allows consideration of cefiderocol as a true alternative agent for difficult-to-treat infections caused by carbapenem-resistant *P. aeruginosa* in Peru, and these data can probably be extrapolated to neighbouring countries.[40] Nevertheless, it is necessary to highlight again the need for its judicious use, considering cefiderocol as a last-resort antimicrobial agent and establishing cefiderocol susceptibility levels whenever possible.

No data about clonality of the included isolates were obtained, with this being the main limitation of the study. Nevertheless, the isolates were recovered in nine different health centres, which together with the high diversity of *oprD* alterations, strongly suggests a high clonal diversity.

In summary, the present results describe the activity of cefiderocol against extensively resistant clinical isolates of *P. aeruginosa* in Peru, suggesting its potential role in the treatment of severe infections in this country.

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Transparency declarations

Cefiderocol is owned by Shionogi & Co. Ltd.

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