Imipenem-relebactam activity and genotypic characteristics of carbapenem-resistant *Enterobacterales* and *Pseudomonas aeruginosa* isolates from Latin American infections – Study for Monitoring Antimicrobial Resistance Trends (SMART) 2017-2020

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Background

Imipenem/relebactam (IMI/REL) is a combination of imipenem/cilastatin (IMI) with relebactam, an inhibitor of class A and C β-lactamases, and has been approved in the US and EU, but not in Latin America.

This report evaluates the in vitro activity of IMI/REL and comparators against Latin America (LATAM) *Enterobacterales* and *P. aeruginosa* (PSA) and the frequency of carbapenemase encoding genes (CEG) among gram-negative bacilli (GNB) isolated from LATAM through the SMART program (2017-2020).

Methods

There were 21,606 GNB isolates collected in 10 LATAM countries (2017-2020). MICs for amikacin (AK), ceftazidime-avibactam (C-A), ceftolozane/tazobactam (C/T), and IMI/REL were determined by broth microdilution and interpreted by CLSI. A subset of carbapenem-resistant *Enterobacterales* and *P. aeruginosa* was selected for characterization of carbapenemase encoding genes by PCR followed by DNA sequencing.

Results

Escherichia coli (N=9,872; EC) tested susceptible to >96% of all antibiotics analyzed; for *P. aeruginosa* (N=4,528), C/T and C-A had the best susceptibility rates (85.7% and 86.6%, respectively); for *Enterobacter cloacae* (N=1,091; ECL) and *Klebsiella pneumoniae* (N=6,115; KPN), we note that only IMI/REL and C-A were ≥95% susceptible.

Table 1. Antimicrobial susceptibility of *Enterobacterales* and *P. aeruginosa* (full data analysis = 21,606)

Species	N=21,606	Amikacin	Ceftazidime-avibactam	Ceftolozane/tazobactam	Imipenem/relebactam
Enterobacter cloacae	1,091	1,034 (94.8%)	796 (95.7%)	815 (74.7%)	1,048 (96.1%)
Escherichia coli	9,872	9,723 (98.5%)	7,441 (99.4%)	9,495 (96.2%)	9,804 (99.3%)
Klebsiella pneumoniae	6,115	5,580 (91.2%)	4,616 (95.6%)	4,250 (69.5%)	5,789 (94.7%)
Pseudomonas aeruginosa	4,528	3,825 (84.5%)	3,095 (86.6%)	3,882 (85.7%)	3,645 (80.5%)

Note: C-A MICs are only reported from 2018-2020. Thus, the total number of isolates for which the in vitro susceptibility was tested is different.

The profile of 2,845 carbapenem-resistant isolates was analyzed and the main isolated agent in most countries was KPN, corresponding to 55% (1,470), except in Mexico, Panama, and Venezuela, where PSA was the main carbapenemase producer.

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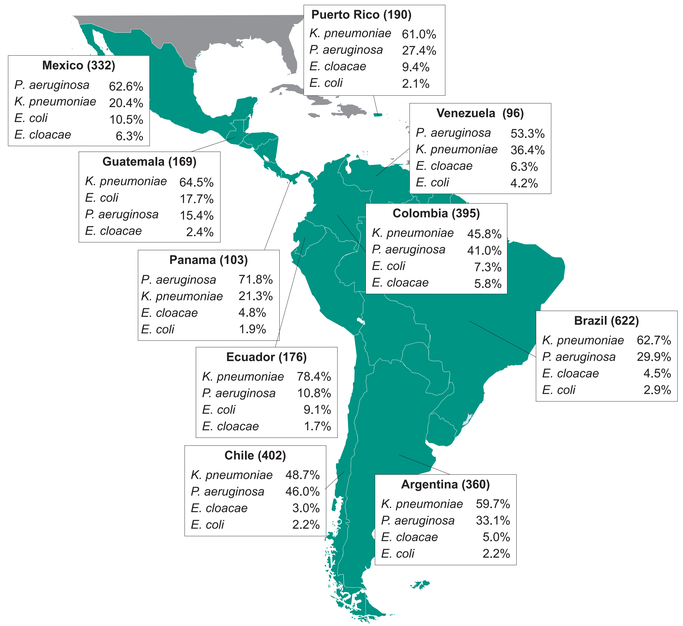
Figure 1. Most common carbapenemase-producing bacteria in LATAM (n = 2,845)



According to table 2, the $bla_{\text{kpc-2,3}}$ were found in KPN as follow: 85.1%, 80.2%, 86.2%, 83.3% and 96.5% in Argentina, Brazil, Colombia, Ecuador, and Puerto Rico, respectively; Guatemala, Mexico, and Venezuela presented $bla_{\text{NDM-1}}$ in 74.3%, 44.1%, and 51.4%, respectively.

Among ECL, $bla_{\text{KPC-2}}$ (35.7%-Brazil, 60.9%-Colombia) and $bla_{\text{NDM-1}}$ (45.7%-Mexico, 50.0%-Venezuela) were most frequent, $bla_{\text{IMP-18}}$ (38.8%) were observed in Puerto Rico and we observed first-time-reported $bla_{\text{kpc-45}}$ in 27.7%.

PSA expressed $bla_{\text{kpc-2}}$ in Colombia (33.3%), $bla_{\text{VIM-2}}$ in Chile and Venezuela (44.3%, 58.8%) and $bla_{\text{spm-1}}$ occurring only in Brazil (6.9%).

Table 2. Most frequent CEG detected among carbapenemase-resistant isolates in Latin American countries (genotypical sample analyzed n = 2,845)*

Country	Carbapenem-resistant bacteria (n - %)	Main Carbapenemase (%)
Argentina	*K. pneumoniae* (215 - 59.7%) *P. aeruginosa* (119 - 33.1%) *E. cloacae* (18 - 5.0%) *E. coli* (8 - 2.2%)	KPC-2 (76.4%) VIM-2 (3.4%) KPC-2 (38.9%) KPC-type (25.0%)
Brazil	*K. pneumoniae* (390 – 62.7%) *P. aeruginosa* (186 - 29.9%) *E. cloacae* (28 - 4.5%) *E. coli* (18 - 2.9%)	KPC-2 (79.2%) SPM-1 (6.9%) KPC-2 (35.7%) KPC-2 (77.8%)
Chile	*K. pneumoniae* (196 – 48.7%) *P. aeruginosa* (185 – 46.0%) *E. cloacae* (12 – 3.0%) *E. coli* (9 - 2.2%)	KPC-2 (11.2%) VIM-2 (44.3%) VIM-1 (25.0%) KPC-2 (11.1%)
Colombia	*K. pneumoniae* (181 – 45.8%) *P. aeruginosa* (162 – 41.0%) *E. coli* (29 - 7.3%) *E. cloacae* (23 – 5.8%)	KPC-3 (53.0%) KPC-2 (33.3%) KPC-2 (65.5%) KPC-2 (60.9%)
Guatemala	*K. pneumoniae* (109 – 64.5%) E. coli (30 - 17.7%) *P. aeruginosa* (26 – 15.4%) *E. cloacae* (4 – 2.4%)	NDM-1 (74.3%) NDM-1 (66.6%) KPC-2 (19.2%) NDM-1 (75.0%)
Mexico	*P. aeruginosa* (208 – 62.6%) *K. pneumoniae* (68 – 20.4%) *E. coli* (35 - 10.5%) *E. cloacae* (21 – 6.3%)	VIM-2 (8.6%) NDM-1 (44.1%) NDM-5 (31.4%) NDM-1 (45.7%)
Panama	*P. aeruginosa* (74 – 71.8%) *K. pneumoniae* (22 – 21.3%) *E. cloacae* (5 – 4.8%) *E. coli* (2 - 1.9%)	VIM-2 (25.7%) KPC-3 (45.4%) NDM-1 (20.0%) NDM-1 (50.0%)
Ecuador	*K. pneumoniae* (138 – 78.4%) *P. aeruginosa* (19 - 10.8%) *E. coli* (16 - 9.1%) *E. cloacae* (3 - 1.7%)	KPC-2 (52.2%) VIM-2 (5.3%) KPC-2 (31.2%) KPC-2 (33.3%)
Puerto Rico	*K. pneumoniae* (116 – 61.0%) *P. aeruginosa* (52 - 27.4%) *E. cloacae* (18 - 9.4%) *E. coli* (4 - 2.1%)	KPC-2 (85.3%) KPC-2 (19.2%) KPC-2 (38.8%), KPC-45 (27.7%) and IMP-18 (38.8%) KPC-2 (100%)
Venezuela	*P. aeruginosa* (51 – 53.3%) *K. pneumoniae* (35 – 36.4%) *E. cloacae* (6 – 6.3%) *E. coli* (4 - 4.2%)	VIM-2 (58.8%) NDM-1 (51.4%) NDM-1 (50.0%) NDM-1 (50.0 %)

*It was not possible to determine if the isolate have one or more genes.

Conclusions

The frequency of CEG is a threat in LATAM, mostly in *Enterobacterales*, whereas PSA as expected, has a lower frequency, but is still a concern in some countries. It was also noted that in all countries, except Colombia, Ecuador and Puerto Rico, the most prevalent carbapenemase for PSA was class B enzymes. In the LATAM scenario, IMI/REL has shown relevant activity against CEG producers, showing it is an option for treatment infections caused by MDR strains.

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