ID 910367

Frequency of Carbapenemase-Encoding Genes among Imipenem-Resistant Gram-Negative Bacilli Isolated from Latin America: Is there a Role for Imipenem/Relebactam? Results from SMART 2017-2018

Gales, A.C.[1]; Beirão, E.M.[2]; Tuon, F.F.[3]; Rodrigues, S.S.[4]; Andrade, T.K.[4]; Serra, F.B. [4]; de Paula, M.D.N.[4]; Polis, T.J.[4].

[1]UNIFESP, Division of Infectious Diseases, Departament of Internal Medicine, Escola Paulista de Medicina - EPM, São Paulo, Brazil
[2]Mandaqui Hospital, São Paulo, Brazil
[3]Laboratory of Emerging Infectious Diseases, School of Medicina, Pontifícia Universidade Catolica do Paraná, Curitiba, Brazil
[4]Global Medical Affairs, MSD in Brazil, São Paulo, Brazil

INTRODUCTION

Gram-negative bacterial (GNB) infections have become increasingly difficult to treat due to raising antimicrobial resistance rates in certain geographic regions such as Latin America[1,2]. Imipenem/relebactam (IMI/REL) is a novel beta-lactam/beta-lactamase inhibitor combination that was recently developed for clinical use to overcome the emergence and spread of carbapenemase-producing Enterobacterales[3]. IMI/REL was recently approved in the USA but it is not available in Latin America yet. The Study for Monitoring Antimicrobial Resistance Trends (SMART) evaluates the in vitro activity of various GNB against selected antimicrobial agents since 2002 and includes IMI/REL since 2015.

The objective of this analysis was to gain insight of the possible therapeutic role of IMI/REL in this region, evaluating the activity of IMI/REL and comparator agents against the four most frequent GNB isolates and the frequency of carbapenemase-encoding genes (CEG) among imipenem-resistant GNB and PSA isolated from Latin America through the SMART Program from 2017-2018.

METHODS

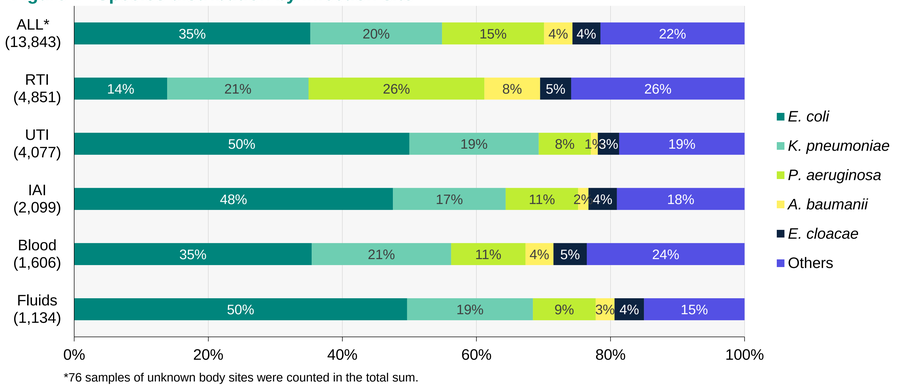
13,843 GNB isolates including Enterobacterales (ENT) and *P. aeruginosa* (PSA) were collected from 36 medical sites of 10 Latin American countries during 2017-2018. Each site collected up to the indicated number of isolates in 2017/2018 from lower respiratory tract infections (RTI) (100/100), complicated urinary infections (cUTI) (75/50), complicated intra-abdominal infections (cIAI) (75/50) and blood (50 only in 2018).

Samples were consecutive and non-duplicate. MICs were determined using CLSI broth microdilution and also interpreted by CLSI criteria, except for IMI/REL, where United States Food and Drug Administration (US FDA) breakpoints were applied.

A subset of IMI-resistant isolates were selected for characterization of carbapenemase encoding genes via multiplex PCR and DNA sequencing. β-lactamase genes codifying ESBL, carbapenemases, and plasmid-mediated AmpC were investigated in ENT and PSA.

RESULTS

Figure 1. Species distribution by infection site



*76 samples of unknown body sites were counted in the total sum.

Figure 2. Most frequent CEG detected among carbapenemase producing, IMI-resistant Enterobacterales (Panel A), and MBL among *P. aeruginosa* (Panel B) isolates in Latin American countries

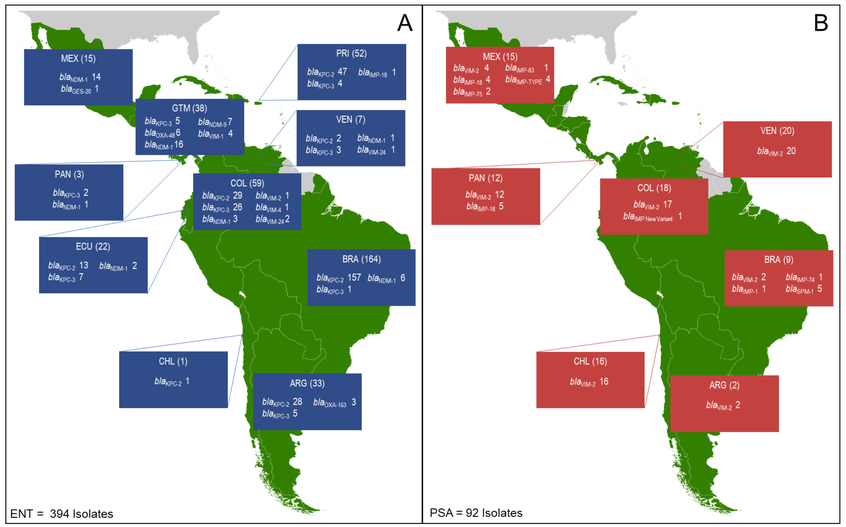


Table 1. Antimicrobial susceptibility to IMI/REL and comparators by enterobacterales and *P. aeruginosa*[a]

Pathogen (n) Antimicrobial Agents	$MIC_{50/90}$	S(%)	I(%)	R(%)
***Escherichia coli* (4877)**				
Amikacin	≤4/8	98.5%	0.8%	0.7%
Ceftazidime	≤1/>16	72.3%	5.4%	22.3%
Colistin	≤1/≤1	99.1%	0.0%	0.9%
Ertapenem	≤0.12/0.12	97.9%	0.5%	1.6%
Imipenem	≤0.5/≤0.5	98.5%	0.4%	1.1%
Imipenem/relebactam[b]	0.12/0.25	99.6%	0.1%	0.3%
Meropenem	0.12/0.12	99.0%	0.2%	0.8%
Piperacillin Tazobactam	≤2/16	90.1%	5.8%	4.1%
***Klebsiella pneumoniae* (2718)**				
Amikacin	≤4/16	93.0%	4.0%	3.0%
Ceftazidime	8/>32	48.3%	4.8%	46.9%
Colistin	≤1/≤1	94.5%	0.0%	5.5%
Ertapenem	0.06/>4	77.4%	0.9%	21.7%
Imipenem	≤0.5/>8	80.9%	1.2%	17.9%
Imipenem/relebactam[b]	0.25/0.5	96.5%	0.8%	2.7%
Meropenem	0.12/>8	79.8%	2.0%	18.2%
Piperacillin Tazobactam	16/>64	58.7%	12.7%	28.6%
***Pseudomonas aeruginosa* (2108)**				
Amikacin	≤4/>32	84.9%	3.6%	11.5%
Ceftazidime	4/>32	71.6%	5.2%	23.2%
Colistin	≤1/≤1	99.8%	0.0%	0.2%
Imipenem	2/32	63.2%	5.1%	31.7%
Imipenem/relebactam[b]	0.5/8	82.8%	5.5%	11.7%
Meropenem	1/>16	65.2%	6.0%	28.8%
Piperacillin Tazobactam	8/>64	67.9%	13.9%	18.2%
***Enterobacter cloacae* (578)**				
Amikacin	≤4/8	94.5%	2.4%	3.1%
Ceftazidime	1/>32	62.1%	1.7%	36.2%
Colistin	≤1/≤1	93.6%	0.0%	6.4%
Ertapenem	0.06/2	82.0%	6.4%	11.6%
Imipenem	≤0.5/1	91.0%	2.6%	6.4%
Imipenem/relebactam[b]	0.25/0.5	96.7%	0.3%	3.0%
Meropenem	0.12/0.25	93.1%	1.7%	5.2%
Piperacillin Tazobactam	≤4/>64	72.3%	9.2%	18.5%

[a]Susceptibility values ≥90% shaded in blue
[b]United States Food and Drug Administration (US FDA) breakpoints for imipenem/cilastatin/relebactam were applied to IMI/REL

RESULTS SUMMARY

- *E. coli* was the most frequent species isolated from all body infections, except for RTI infections, where *P. aeruginosa* was the most frequent species. *K. pneumoniae* ranked as the second most frequent pathogen in all body sites infections (Figure 1).
- Among the 422 imipenem-resistant ENT further selected for detection of carbapenemase encoding genes, 394 (93.4%) isolates were detected as carbapenemase producers (Figure 2).
- bla_{KPC-2} and bla_{KPC-3} were the most common CEG found in ENT in all countries except in Guatemala and Mexico. bla_{OXA-48} and $bla_{OXA-163}$ were only detected in Guatemala and Argentina, respectively. bla_{NDM-1} was identified in ENT isolated from all countries except Argentina, Chile and Puerto Rico (Figure 2A).
- A total of 415 imipenem-resistant *P. aeruginosa* were selected for characterization of carbapenemase content. The presence of metallo-beta-lactamase (MBL) encoding gene was confirmed in only 92 (22.2%) of these isolates (Figure 2).
- bla_{VIM-2} was the most common MBL encoding gene identified, except for Ecuador, Guatemala, and Puerto Rico. bla_{IMP} variants were observed in Brazil (bla_{IMP-1}, bla_{IMP-74}), Colombia (a new $bla_{IMP-variant}$), Mexico (bla_{IMP-18} and bla_{IMP-75}, bla_{IMP-83}), and Panama (bla_{IMP-18}). As already expected, bla_{SPM-1} was only encountered in Brazil (Figure 2B).

CONCLUSION

- CEG were frequently detected among imipenem-resistant ENT. In contrast, CEG was less frequently detected in imipenem-resistant *P. aeruginosa*.
- bla_{KPC-2} and bla_{VIM-2} were the most frequent CEG detected in ENT and *P. aeruginosa* isolates collected from Latin American medical centers. However, important local variations were observed in ENT and *P. aeruginosa* isolates with some CEG being detected in specific countries. For example, bla_{SPM-1} was identified only in Brazilian *P. aeruginosa* isolates, while bla_{OXA-48} and its derivatives only found in ENT isolated from Argentina and Guatemala.
- IMI/REL showed relevant in vitro activity against the most frequent ENT and *P. aeruginosa* isolates and will represent an important addition to the therapeutic options to treat GNB infections in Latin America.

References and Acknowledgements

1. Villegas MV, Pallares CJ, Escandón-Vargas K, Hernández-Gómez C, Correa A, Álvarez C, et al. (2016) Characterization and Clinical Impact of Bloodstream Infection Caused by Carbapenemase-Producing Enterobacteriaceae in Seven Latin American Countries. PLoS ONE 11(4): e0154092. https://doi.org/10.1371/journal.pone.0154092
2. Leal, H.F., Azevedo, J., Silva, G.E.O. et al. Bloodstream infections caused by multidrug-resistant gram-negative bacteria: epidemiological, clinical and microbiological features. BMC Infect Dis 19, 609 (2019). https://doi.org/10.1186/s12879-019-4265-z
3. A Comparison of Treatment Outcomes Between Analysis Populations in the RESTORE-IMI 1 Phase 3 Trial of Imipenem/Cilastatin/Relebactam Versus Colistin Plus Imipenem/Cilastatin in Patients With Imipenem-Nonsusceptible Bacterial Infections Keith S. Kaye, Helen W. Boucher, Michelle L. Brown, Angela Aggrey, Ireen Khan, Hee-Koung Joeng, Robert W. Tipping, Jiejun Du, Katherine Young, Joan R. Butterton, Amanda Paschke Antimicrobial Agents and Chemotherapy Feb 2020, AAC.02203-19; DOI: 10.1128/AAC.02203-19

We would like deeply thank the participants of the SMART program for their continuing contributions to its success. Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

https://bit.ly/3h8kcfB