Global Prevalence of Colistin- and Carbapenem-Resistant Gram-Negative Organisms: SMART 2015-2016

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INTRODUCTION

Antimicrobial resistance is spreading worldwide, including acquired resistance to carbapenems, requiring the increasing use of older agents like colistin (CST). In this study, we analyzed the global prevalence of carbapenem-resistant (CR) gram-negative clinical isolates that were also resistant to CST.

METHODS

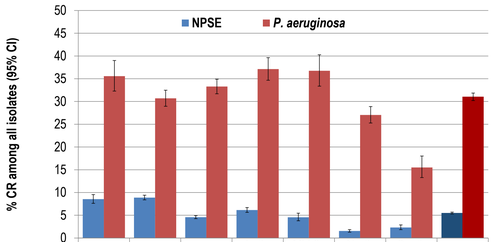
In 2015-2016, 170 hospitals in 53 countries collected consecutive gram-negative aerobic or facultative bacilli from intra-abdominal, urinary, and respiratory tract infections. MICs were determined for 45,126 non-Proteeae non-Serratia Enterobacteriaceae (NPSE) and 11,026 P. aeruginosa isolates using CLSI broth microdilution [1,2]. As our interest was in acquired resistance, Proteeae and Serratia spp. were excluded due to intrinsic non-susceptibility to imipenem and/or CST.

The % susceptible was assessed using CLSI breakpoints where available. For comparison purposes, imipenem susceptible breakpoints of ≤1 mg/L (NPSE) and ≤2 mg/L (P. aeruginosa) were applied to imipenem/relebactam. The EUCAST CST breakpoint of ≤2 mg/L was used for NPSE [3]. Isolates with MICs above the CLSI susceptible breakpoint for imipenem were defined as CR.

All NPSE and P. aeruginosa isolates non-susceptible to imipenem from all countries except China and India were tested for the presence of genes encoding ESBLs, carbapenemases, and AmpC cephalosporinases using published multiplex PCR assays, followed by full-gene DNA sequencing.

RESULTS

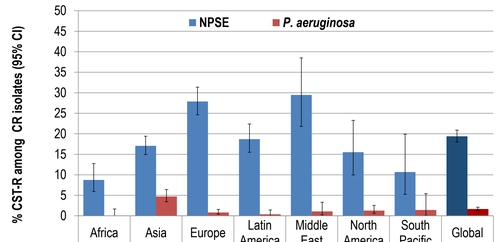
Figure 1. Prevalence of carbapenem-resistance among all NPSE and *P. aeruginosa*[a]



	Africa	Asia	Europe	Latin America	Middle East	North America	South Pacific	Global
NPSE	8.5	8.9	4.6	6.2	4.6	1.5	2.3	5.5
P. aeruginosa	35.6	30.7	33.3	37.1	36.8	27.0	15.5	31.0

[a] Total number of isolates (NPSE, P. aeruginosa): Africa (3209, 773), Asia (12202, 2623), Europe (14798, 3338), Latin America (8000, 1452), Middle East (2460, 751), North America (7529, 2330), South Pacific (3249, 903), Global (51447, 12170)

Figure 2. Prevalence of colistin-resistance among carbapenem-resistant NPSE and *P. aeruginosa*[a]



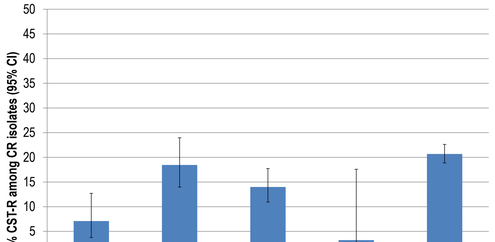
	Africa	Asia	Europe	Latin America	Middle East	North America	South Pacific	Global
NPSE	8.8	17.1	27.9	18.7	29.5	15.5	10.7	19.4
P. aeruginosa	0.0	4.7	0.8	0.4	1.1	1.3	1.4	1.6

[a] Number of carbapenem-resistant isolates (NPSE, P. aeruginosa): Africa (274, 275), Asia (1084, 805), Europe (678, 1111), Latin America (492, 539), Middle East (112, 276), North America (116, 630), South Pacific (75, 140), Global (2831, 3776)

Table 1. Prevalence of combined colistin- and carbapenem-resistance among all NPSE and *P. aeruginosa*

	% colistin- and carbapenem-resistant (total no. of isolates)							
	Africa	Asia	Europe	Latin America	Middle East	North America	South Pacific	Global
NPSE	0.7 (3209)	1.5 (12202)	1.3 (14798)	1.2 (8000)	1.3 (2460)	0.2 (7529)	0.2 (3249)	1.1 (51447)
P. aeruginosa	0.0 (773)	1.4 (2623)	0.3 (3338)	0.1 (1452)	0.4 (751)	0.3 (2330)	0.2 (903)	0.5 (12170)

Figure 3. Prevalence of colistin-resistance among carbapenem-resistant isolates in the 5 most common NPSE species



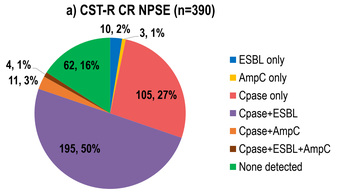
	E. aerogenes (n=141)	E. cloacae (n=233)	E. coli (n=407)	K. oxytoca (n=31)	K. pneumoniae (n=1793)
%	7.1	18.5	14.0	3.2	20.7

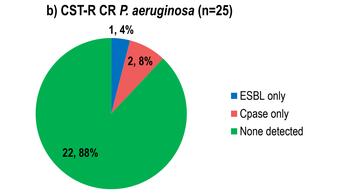
Table 2. Global susceptibility of isolates with combined colistin- and carbapenem-resistance

Antimicrobial agent	% S	% I	% R	MIC_{50}	MIC_{50}	MIC range
NPSE (n=549)						
Amikacin	59.2	9.7	31.2	16	>32	≤4 - >32
Aztreonam	20.2	0.9	78.9	>16	>16	≤1 - >16
Cefepime	18.8	4.0	77.2	>32	>32	≤1 - >32
Ceftazidime	19.9	2.4	77.8	>32	>32	≤0.5 - >32
Ceftolozane-Tazobactam[a]	23.9	1.9	74.2	>32	>32	≤0.06 - >32
Ciprofloxacin	19.7	2.7	77.6	>2	>2	≤0.25 - >2
Imipenem-Relebactam	49.5	11.8	38.6	2	>32	0.12 - >32
Levofloxacin	23.3	3.1	73.6	>4	>4	≤0.5 - >4
Piperacillin-Tazobactam	21.1	3.8	75.1	>64	>64	≤2 - >64
***P. aeruginosa* (n=62)**						
Amikacin	35.5	8.1	56.5	>32	>32	≤4 - >32
Aztreonam	19.4	9.7	71.0	>16	>16	≤1 - >16
Cefepime	29.0	9.7	61.3	>32	>32	≤1 - >32
Ceftazidime	30.7	3.2	66.1	>32	>32	≤0.5 - >32
Ceftolozane-Tazobactam[b]	46.3	12.2	41.5	8	>32	0.5 - >32
Ciprofloxacin	21.0	14.5	64.5	>2	>2	≤0.25 - >2
Imipenem-Relebactam	43.5	12.9	43.5	4	>32	0.5 - >32
Levofloxacin	27.4	17.7	54.8	>4	>4	≤0.5 - >4
Piperacillin-Tazobactam	25.8	12.9	61.3	>64	>64	≤2 - >64

[a] Only tested in 2016 (n=310)
[b] Only tested in 2016 (n=41)

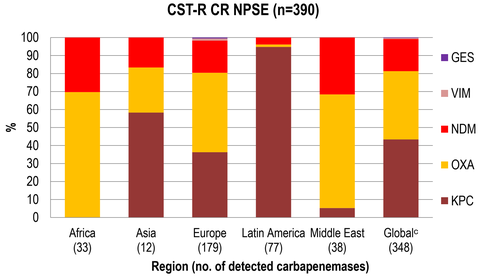
Figure 4 a and b. Acquired β-lactamases detected in characterized global isolates with combined colistin- and carbapenem-resistance (number of isolates, % of total)[a b]





[a] Isolates from China and India were not available for molecular characterization.
[b] Original spectrum β-lactamases (e.g., TEM-1) and intrinsic chromosomally-encoded AmpC β-lactamases common to Enterobacter spp., Citrobacter spp., and P. aeruginosa are not included in the analysis.

Figure 5. Carbapenemase types detected in NPSE isolates with combined colistin- and carbapenem-resistance (showing only regions with at least 10 detected carbapenemases)[a b]



[a] Isolates from China and India were not available for molecular characterization.
[b] Includes isolates carrying more than one carbapenemase gene.
[c] Includes carbapenemases from isolates collected in North America (4 KPC, 2 OXA-48-like, 1 NDM) and South Pacific (2 NDM).

RESULTS SUMMARY

- Prevalence of CR NPSE ranged from 1.5% in North America to 8.9% in Asia and prevalence of CR P. aeruginosa from 15.5% in South Pacific to 37.1% in Latin America (Figure 1)
- Among CR NPSE isolates, colistin-resistance ranged from 8.8% in Africa to 29.5% in the Middle East and was highest in K. pneumoniae (20.7%) (Figures 2 and 3); among CR P. aeruginosa, colistin-resistance ranged from 0% in Africa to 4.7% in Asia (Figure 2)
- The prevalence of CST-R CR isolates was ≤1.5% in all regions (Table 1)
- Susceptibility of CST-R CR isolates to all studied agents was <60%; amikacin (59.2%) and imipenem-relebactam (49.5%) were the most active agents in vitro against NPSE, and ceftolozane-tazobactam (46.3%) and imipenem/relebactam (43.6%) against P. aeruginosa (Table 2)
- The majority of CST-R CR NPSE isolates (81%) carried carbapenemases with or without ESBL and AmpC; the majority of CR CST-R P. aeruginosa (88%) carried no detectable acquired β-lactamases (Figure 4)
- KPC was the predominant carbapenemase in Latin America and Asia (without China or India); OXA-48-like was the most common carbapenemase type in Africa, Europe, and the Middle East; and NDM was the second most common carbapenemase in Africa and Middle East (Figure 5)

CONCLUSIONS

Combined colistin- and carbapenem-resistance was rare in P. aeruginosa, but was detected in a small yet significant proportion of NPSE, especially from Europe and the Middle East, where almost 30% of CR NPSE were also CST-R. New antimicrobial agents with activity against multidrug-resistant isolates are needed.

References and Acknowledgments:

1. Clinical and Laboratory Standards Institute. 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Tenth Edition. CLSI document M07-A10 (ISBN 1-56238-987-4). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
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3. The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints 2017; http://www.eucast.org/clinical_breakpoints/

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