C-171

Ertapenem and imipenem MIC distributions of carbapenemase-positive *Enterobacteriaceae* from SMART

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Revised Abstract

Background: Carbapenemases (Cpases) are spreading, but their detection can be difficult if they result in low or no reduction in susceptibility to carbapenems. Thus their prevalence may be underestimated. Using data from the Study for Monitoring Antimicrobial Resistance Trends (SMART), the proportion of Cpase+ *Enterobacteriaceae* susceptible (S) to ertapenem (ETP) or imipenem (IPM) was examined. **Methods:** 86,833 *Enterobacteriaceae* isolates from intra-abdominal or urinary tract infections were collected in 44 countries in 2008-2013, of which 1,178 were Cpase+ (1.4%). MICs were determined and phenotypic ESBL (ESBLp) status confirmed by CLSI broth microdilution method. All ETP non-susceptible (NS) *Enterobacteriaceae* and a random sample of ~60% ESBLp+ *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis* isolates were molecularly characterized for β-lactamase genes.
Results: MIC frequency distribution [n (%)] of Cpase+ *Enterobacteriaceae*:

	MIC (μg/mL)								
	≤0.06	0.12	0.25	0.5	1	2	4	>4	Total n
Ertapenem									
KPC					9 (1.4)	24 (3.8)	32 (5.1)	563 (89.6)	628
MBL	1 (0.3)			4 (1.2)	17 (5.1)	23 (6.9)	13 (3.9)	277 (82.7)	335
OXA-48-like		1 (0.4)		1 (0.4)	33 (14.3)	40 (17.3)	37 (16.0)	119 (51.5)	231
GES				1 (50.0)				1 (50.0)	2
Imipenem									
KPC				2 (0.3)	15 (2.4)	47 (7.5)	79 (12.6)	485 (77.2)	628
MBL		1 (0.3)	1 (0.3)	1 (0.3)	7 (2.1)	29 (8.7)	48 (14.3)	248 (74.0)	335
OXA-48-like		1 (0.4)	7 (3.0)	16 (6.9)	64 (27.7)	81 (35.1)	29 (12.6)	33 (14.3)	231
GES					1 (50.0)			1 (50.0)	2

MICs in the susceptible range (CLSI 2015) are shaded. MBL, metallo-β-lactamase.

Overall, 9.8% of Cpase producers were IPM-S and 0.7% were ETP-S. These numbers are likely somewhat underestimated, since the only way our testing protocol allowed identification of ETP-S Cpase producers was through characterization of a sample of ESBLp+ isolates. ESBLp– ETP-S isolates are not characterized and any Cpases they may carry would not be detected. Similarly, IPM-S Cpase producers would only be characterized if they were ETP-NS or among the characterized ESBLp+ sample. However, ETP is generally the carbapenem with the lowest activity against Cpase producers and therefore the most sensitive globally-available indicator of Cpase activity. **Conclusions:** Cpase producers, especially those with OXA-48 enzymes, can exhibit low-level resistance or even susceptibility to carbapenems, making it more difficult to identify them.

Introduction

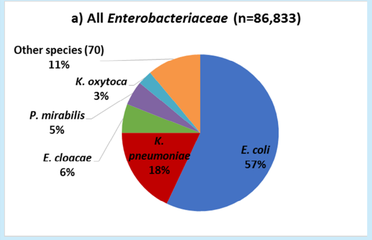
Carbapenemases (Cpases) are spreading, but their detection can be difficult if they result in low or no reduction in susceptibility to carbapenems. Thus their prevalence may be underestimated. Using data from the Study for Monitoring Antimicrobial Resistance Trends (SMART), the proportion of Cpase+ *Enterobacteriaceae* susceptible (S) to ertapenem (ETP) or imipenem (IPM) was examined.

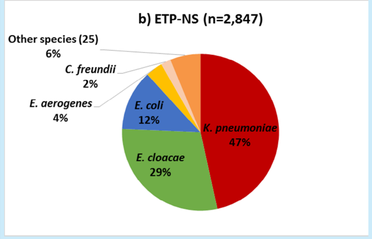
Materials & Methods

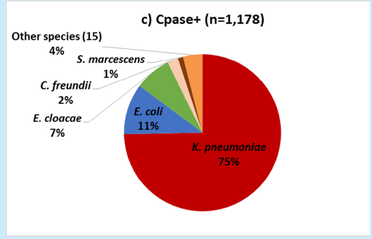
- 86,833 *Enterobacteriaceae* isolates collected in 44 countries in 2008-2013 from intra-abdominal or urinary tract infections were available for this study.
- Isolates from China (all years) and India (most of 2010, 2011-2013) were excluded from analysis because they were not available for molecular characterization due to export restrictions.
- MICs were determined and extended-spectrum b-lactamase phenotype (ESBLp) was confirmed by CLSI broth microdilution [1, 2]. MICs were interpreted according to current CLSI criteria [2].
- ETP non-susceptible (NS) *Enterobacteriaceae* and a random sample of ~60% ESBLp+ *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* isolates were screened for the presence of β-lactamase genes encoding ESBLs, AmpC, and carbapenemases (KPC, OXA-48, NDM, VIM, and IMP) using the Check-MDR CT101 microarray (Check-Points, Wageningen, the Netherlands) and PCR assays, followed by sequencing.
- CLSI interpretive criteria for ETP changed during the course of this study. Isolates collected in 2008-2010 that tested with ETP MIC >0.25 μg/mL were molecularly characterized according to the CLSI interpretive criteria in place at the time of testing (M100-S20-U, M100-S21). Isolates collected in 2011-2013 were characterized if ETP MIC >0.5 μg/mL (M100-S22).

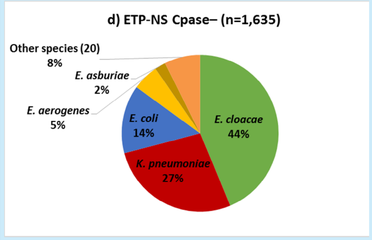
Results

Figure 1 a-d. Species distribution of *Enterobacteriaceae* (and ertapenem non-susceptible and Cpase subsets) collected in 2008-2013.









ETP-NS, ertapenem non-susceptible; Cpase, carbapenemase.

Table 1. Geographical distribution of *Enterobacteriaceae* and ertapenem non-susceptible and Cpase subsets) collected in 2008-2013.

	Total n	n (%) All ETP-NS[a]	Cpase+[b, d]	ETP-NS Cpase–[c, d]
All[e]	**86,833**	**2,847 (3.3)**	**1,178 (1.4)**	**1,635 (1.9)**
Africa	3,914	112 (2.9)	70 (1.8)	43 (1.1)
Asia[e]	14,940	579 (3.9)	161 (1.1)	412 (2.8)
Europe	27,969	801 (2.9)	356 (1.3)	431 (1.5)
Latin America	16,115	691 (4.3)	340 (2.1)	350 (2.2)
Middle East	3,470	136 (3.9)	86 (2.5)	48 (1.4)
North America	14,708	404 (2.7)	128 (0.9)	264 (1.8)
South Pacific	5,717	124 (2.2)	37 (0.6)	87 (1.5)

ETP-NS, ertapenem non-susceptible; Cpase, carbapenemase.
[a] Based on CLSI 2015 breakpoints (ETP >0.5 μg/mL) .
[b] Cpase+, isolates in which a gene encoding a carbapenemase was detected by microarray or PCR. Includes 8 ETP-S isolates.
[c] Cpase–, isolates in which no gene encoding a carbapenemase was detected. 96.5% of these isolates carried a plasmid- or chromosomally-mediated b-lactamase presumably combined with a permeability defect that could account for the observed phenotype.
[d] The sum of Cpase+ and ETP-NS Cpase– isolates is smaller than the total number of ETP-NS isolates because 42 ETP-NS isolates were not available for molecular characterization.
[e] Includes 1132 isolates collected from India in 2008-2010. Does not include isolates from China.

Table 3. Imipenem MIC frequency distribution [n (%)] when tested against Cpase+ *Enterobacteriaceae*, by species.

	Imipenem MIC (μg/mL) ≤0.06	0.12	0.25	0.5	1	2	4	>4	Total n
E. coli									
All Cpase+		**1 (0.8)**	**4 (3.2)**	**3 (2.4)**	**20 (16.1)**	**21 (16.9)**	**17 (13.7)**	**58 (46.8)**	**124**
KPC				1 (2.9)	3 (8.6)	11 (31.4)	5 (14.3)	15 (42.9)	35
NDM						1 (2.0)	6 (12.2)	42 (85.7)	49
IMP		1 (33.3)					2 (66.7)		3
VIM							1 (100)		1
OXA-48-like			4 (10.8)	2 (5.4)	17 (45.9)	9 (24.3)	3 (8.1)	2 (5.4)	37
K. pneumoniae									
All Cpase+		**1 (0.1)**	**4 (0.5)**	**13 (1.5)**	**46 (5.2)**	**108 (12.3)**	**110 (12.5)**	**598 (68.0)**	**880**
KPC				1 (0.2)	6 (1.1)	28 (5.2)	66 (12.2)	440 (81.3)	541
NDM							9 (7.8)	107 (92.2)	116
IMP			1 (4.2)	1 (4.2)	2 (8.3)	13 (54.2)	3 (12.5)	4 (16.7)	24
VIM						3 (6.5)	8 (17.4)	35 (76.1)	46
OXA-48-like		1 (0.6)	3 (1.8)	11 (6.6)	38 (22.9)	64 (38.6)	24 (14.5)	25 (15.1)	166
GES-5					1 (100)				1
E. cloacae									
All Cpase+			**2 (2.3)**	**10 (11.4)**	**14 (15.9)**	**15 (17.0)**	**47 (53.4)**		**88**
KPC				2 (12.5)		2 (12.5)	2 (12.5)	10 (62.5)	16
NDM						1 (3.2)	3 (9.7)	27 (87.1)	31
IMP					1 (20.0)	3 (60.0)		1 (20.0)	5
VIM					4 (14.8)	5 (18.5)	9 (33.3)	9 (33.3)	27
OXA-48-like			2 (16.7)	3 (25.0)	3 (25.0)	1 (8.3)	3 (25.0)		12

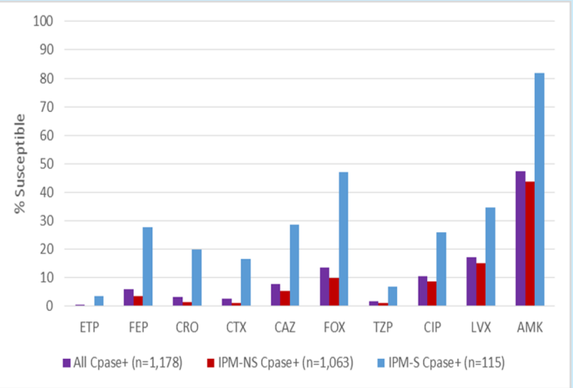
MICs in the susceptible range (CLSI 2015) are shaded.

Table 2. Ertapenem and imipenem MIC frequency distributions [n (%)] when tested against Cpase+ and ETP-NS Cpase– *Enterobacteriaceae*.

	MIC (μg/mL) ≤0.06	0.12	0.25	0.5	1	2	4	>4	Total n
Ertapenem									
All Cpase+	**1 (0.1)**	**1 (0.1)**		**6 (0.5)**	**59 (5.0)**	**86 (7.3)**	**82 (7.0)**	**943 (80.1)**	**1,178**
KPC					9 (1.4)	24 (3.8)	32 (5.1)	563 (89.6)	628
NDM					1 (0.5)	2 (0.9)	3 (1.4)	210 (97.2)	216
IMP				1 (2.8)		5 (13.9)	6 (16.7)	24 (66.7)	36
VIM	1 (1.2)			3 (3.6)	16 (19.3)	16 (19.3)	4 (4.8)	43 (51.8)	83
OXA-48-like		1 (0.4)		1 (0.4)	33 (14.3)	40 (17.3)	37 (16.0)	119 (51.5)	231
GES-5				1 (50.0)				1 (50.0)	2
ETP-NS Cpase–					**786 (48.1)**	**374 (22.9)**	**153 (9.4)**	**322 (19.7)**	**1,635**
Imipenem									
All Cpase+		**2 (0.2)**	**8 (0.7)**	**19 (1.6)**	**86 (7.3)**	**157 (13.3)**	**156 (13.2)**	**750 (63.7)**	**1,178**
KPC				2 (0.3)	15 (2.4)	47 (7.5)	79 (12.6)	485 (77.2)	628
NDM						2 (0.9)	19 (8.8)	195 (90.3)	216
IMP		1 (2.8)	1 (2.8)	1 (2.8)	3 (8.3)	18 (50.0)	6 (16.7)	6 (16.7)	36
VIM					4 (4.8)	9 (10.8)	23 (27.7)	47 (56.6)	83
OXA-48-like		1 (0.4)	7 (3.0)	16 (6.9)	64 (27.7)	81 (35.1)	29 (12.6)	33 (14.3)	231
GES-5					1 (50.0)			1 (50.0)	2
ETP-NS Cpase–	**7 (0.4)**	**138 (8.4)**	**381 (23.3)**	**477 (29.2)**	**373 (22.8)**	**119 (7.3)**	**45 (2.8)**	**95 (5.8)**	**1,635**

MICs in the susceptible range (CLSI 2015) are shaded.
ETP-S, CPase+ isolates (n): VIM-1 (4); IMP-26 (1); OXA-48 (1); OXA-163 (1); GES-5 (1).
The 4 OXA-163 isolates had ETP MICs of 0.12, 1, 2, and >4 μg/mL and IPM MICs of 0.12, 0.25 (2), and 1 μg/mL.
Eighteen isolates carried 2 Cpases: KPC+VIM (Greece, 3); KPC+OXA-48-like (Argentina, 1; Italy, 1; Morocco, 1); NDM+OXA-48-like (Egypt, 4; India, 2; Jordan, 1; Romania, 1; United Arab Emirates, 2; Vietnam, 1); VIM+OXA-48-like (Turkey, 1).

Figure 2. Activity of ertapenem and comparator agents against Cpase+ *Enterobacteriaceae* (including imipenem non-susceptible and susceptible subsets).



ETP, ertapenem; FEP, cefepime; CRO, ceftriaxone; CTX, cefotaxime; CAZ, ceftazidime; FOX, cefoxitin; CIP, ciprofloxacin; LVX, levofloxacin; TZP, piperacillin-tazobactam; AMK, amikacin; IPM, imipenem; NS, non-susceptible; S, susceptible.

Results Summary

- Of the *Enterobacteriaceae* collected as part of the SMART program in 2008-2013, 3.3% were ETP-NS (ranging from 2.2% in South Pacific to 4.3% in Latin America). 1.4% of *Enterobacteriaceae* were Cpase+ (ranging from 0.6% in South Pacific to 2.5% in the Middle East), whereas no Cpase genes were detected in the remaining ETP-NS isolates (1.9% of *Enterobacteriaceae*) (**Table 1**).
- The most common species among ETP-NS and among Cpase+ isolates was *K. pneumoniae*, while the majority of ETP-NS Cpase– isolates were *Enterobacter* spp. (**Figure 1**).
- Overall, 0.7% of Cpase+ isolates (4 of which carried VIM-1) were ETP-S and 9.8% (mostly OXA-48 producers) were IPM-S (**Table 2**). Of the three most common species, the % IPM-S isolates was highest among Cpase+ *E. coli* (22.6%) (**Table 3**).
- The % Cpase+ and % carbapenem-S Cpase+ *Enterobacteriaceae* are likely underestimated, because our testing protocol allowed detection of ETP-S Cpase producers only through characterization of a sample of ESBLp+ isolates. ESBLp– ETP-S isolates are not characterized, and any Cpases they may carry would not be detected. However, ETP is generally the carbapenem with the lowest activity against Cpase producers and therefore the most sensitive globally-available indicator of Cpase activity.
- The activities of all tested antimicrobial agents against Cpase+ isolates was low, with amikacin showing the greatest activity (47% susceptible) compared to all other agents tested (<18% susceptible). Activities against the subset of Cpase+ IPM-S isolates were increased but still did not exceed 47% susceptible for any agent except amikacin (**Figure 2**).

Conclusions

Cpase producers, especially those with OXA-48 enzymes, can exhibit low-level resistance or even susceptibility to carbapenems, making it more difficult to identify them. Cpase producers, including the imipenem-susceptible subset, generally showed low susceptibility to other tested antimicrobial agents, leaving few treatment options. This situation is especially problematic because the efficacy of carbapenems for treating infections due to Cpase producers with low-level resistance or susceptibility to carbapenems remains debatable [3].

References and Acknowledgments:
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3. Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: the phantom menace. J Antimicrob Chemother. 2012 Jul;67(7):1597-606.

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