Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2012–2017) *P. aeruginosa* Isolates from Hospitalised Patients in European Medical Centres

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INTRODUCTION

- Ceftolozane-tazobactam consists of an antipseudomonal cephalosporin and a well-established β-lactamase inhibitor
  - Ceftolozane-tazobactam is active against many common β-lactam resistance mechanisms employed by *Pseudomonas aeruginosa*, including AmpC production (PDC), up-regulated efflux pumps, and porin reductions (OprD loss)
  - Ceftolozane-tazobactam is approved in >50 countries, including the United States since 2014 and in Europe since 2015, for complicated urinary tract infections/acute pyelonephritis and complicated intra-abdominal infections in combination with metronidazole
  - Clinical treatment trials for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia are currently in progress (clinicaltrials.gov Identifier: NCT02070757)
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) is a global surveillance program that monitors resistance of gram-negative isolates to ceftolozane-tazobactam
  - Data from PACTS for *Pseudomonas aeruginosa* isolates collected consecutively from various infection types in patients hospitalised in Europe from 2012–2017 were analysed for this study

MATERIALS AND METHODS

- A total of 6,633 *P. aeruginosa* isolates were collected from 50 European hospitals in 25 countries over the 6-year period (2012–2017)
- Isolates were tested for susceptibility to ceftolozane-tazobactam by CLSI broth microdilution methodology at JMI Laboratories using EUCAST (2018) interpretive criteria
- Other antibiotics tested were amikacin, cefepime, ceftazidime, colistin, gentamicin, levofloxacin, meropenem, and piperacillin-tazobactam
- The following phenotypes were analysed:
  - Ceftazidime-nonsusceptible, meropenem-nonsusceptible, cefepime-nonsusceptible, piperacillin-tazobactam-nonsusceptible, and β-lactam-nonsusceptible
  - Multidrug-resistant (MDR) isolates were identified as nonsusceptible to 3 or more antimicrobial classes
  - Extensively drug-resistant (XDR) isolates were identified as nonsusceptible to all but ≤2 antimicrobial classes
    - Classes tested included aminoglycosides, antipseudomonal carbapenems, antipseudomonal cephalosporins, quinolones, and antipseudomonal penicillin/β-lactamase inhibitor combination

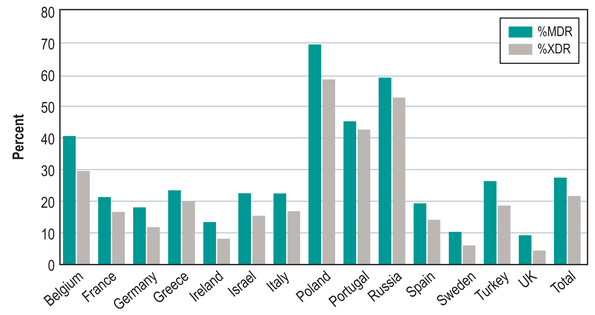
RESULTS

- The 3 most common infection types were pneumonia in hospitalised patients (44.0%) followed by skin and skin structure infection (26.9%), and bloodstream infection (15.5%)
- Ceftolozane-tazobactam and comparator susceptibilities are shown in Table 1 stratified by resistant phenotypes analysed in this study
  - Ceftolozane-tazobactam was the most active β-lactam and second most active antimicrobial tested against resistant phenotypes including MDR isolates
  - Colistin was the most active agent
  - 63.8% of MDR isolates were susceptible to ceftolozane-tazobactam
    - 45.8% were susceptible to amikacin
    - 19.1% were susceptible to meropenem
  - For isolates resistant to the other 4 β-lactams tested, 43.0% were susceptible to ceftolozane-tazobactam
  - The MIC distribution of ceftolozane-tazobactam for all isolates and resistant phenotypes is shown in Table 2
- % MDR isolates varied by country from 9.3% in the United Kingdom to 69.6% in Poland (Figure 1)
  - Two countries had >50% MDR *P. aeruginosa*: Poland, 69.6% and Russia, 59.1%
- The % susceptible for ceftolozane-tazobactam and comparators for 14 countries with >100 isolates are shown in Table 3
  - The % susceptible for ceftolozane-tazobactam varied by country
  - 9 countries had >90% susceptible to ceftolozane-tazobactam
  - Only 2 countries had <70% susceptible (Russia, 60.7% and Portugal, 67.9%)
- Susceptibilities for other drugs also varied by country:
  - Amikacin % susceptible varied from 49.5% in Portugal to 98.6% in the United Kingdom
  - Meropenem % susceptible varied from 25.1% in Poland to 84.6% in Ireland
  - Colistin susceptibility was consistently high; all countries had >98%
- The ceftolozane-tazobactam cumulative percent of MIC by year is shown in Figure 2
  - The number of isolates ≤4 mg/L, the susceptible breakpoint, was relatively stable throughout the study period

CONCLUSIONS

- Ceftolozane-tazobactam demonstrated potent activity against clinical isolates of *P. aeruginosa* from patients in European hospitals from various sites of infection
- The susceptibility for ceftolozane-tazobactam remained stable overall during the 6-year study
- Ceftolozane-tazobactam was the most potent β-lactam and was more active than all comparators, except colistin
- Ceftolozane-tazobactam maintained activity against MDR isolates and against isolates nonsusceptible to all 4 tested β-lactams

Figure 1 Percent of *P. aeruginosa* isolates with MDR (combined nonsusceptibility to ≥3 antibiotic classes) and XDR (nonsusceptible to all but ≤2 classes) by country



Data shown for countries with more than 100 isolates in study

Figure 2 Ceftolozane-tazobactam cumulative percent at each MIC, over 6 years of study

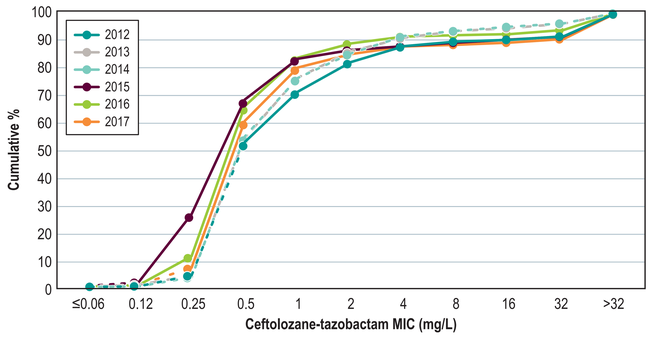


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Table 1 *In vitro* activity of ceftolozane-tazobactam and comparators against *P. aeruginosa* clinical isolates with various resistant phenotypes

		% susceptible[a]							
P. aeruginosa	n	Ceftolozane-tazobactam	Cefepime	Ceftazidime	Meropenem	Piperacillin-tazobactam	Levofloxacin	Amikacin	Colistin
All	6,633	89.6	76.5	74.2	71.0	70.5	61.3	83.6	99.3
MDR	1,827	63.8	26.2	21.0	19.1	9.6	9.0	45.8	98.6
Meropenem-nonsusceptible	1,920	66.5	40.7	38.1	0.0	28.8	20.0	54.0	99.1
Ceftazidime-nonsusceptible	1,713	61.9	23.6	0.0	30.6	6.5	23.4	54.1	98.9
Piperacillin-tazobactam-nonsusceptible	1,956	65.8	28.1	18.1	30.1	0.0	21.7	55.1	99.0
Cefepime-nonsusceptible	1,493	56.8	0.0	12.4	23.7	5.8	15.8	45.8	99.0
β-lactam-nonsusceptible[b]	1,005	43.0	0.0	0.0	0.0	0.0	7.3	35.4	99.2

[a] EUCAST (2018).
[b] Nonsusceptible to 4 β-lactams: ceftazidime, cefepime, piperacillin-tazobactam, and meropenem.

Table 3 *In vitro* activity of ceftolozane-tazobactam and comparators against clinical isolates of *P. aeruginosa* from countries with more than 100 isolates

	% susceptible[a] (number)													
Antimicrobial agent	Belgium (135)	France (784)	Germany (712)	Greece (255)	Ireland (267)	Israel (226)	Italy (769)	Poland (375)	Portugal (274)	Russia (443)	Spain (836)	Sweden (164)	Turkey (561)	UK (291)
Ceftolozane-tazobactam	80.7	97.6	95.4	81.6	99.3	98.2	92.3	81.1	67.9	60.7	95.2	97.6	91.6	99.7
Amikacin	74.1	90.9	93.1	80.0	92.9	94.2	85.3	50.9	70.8	49.0	93.5	97.6	86.1	98.6
Cefepime	64.4	81.9	85.7	77.6	88.0	81.9	82.6	50.9	60.2	49.9	83.1	92.7	79.1	91.4
Ceftazidime	60.0	78.2	82.9	79.2	84.6	74.8	78.7	46.9	55.1	44.5	80.8	85.4	79.1	88.3
Colistin	99.3	99.4	99.9	100.0	98.9	100.0	99.2	98.9	99.6	98.9	99.5	99.4	98.4	100.0
Gentamicin	83.7	82.3	90.7	81.2	90.6	87.6	80.6	45.9	65.7	43.8	83.8	98.2	82.0	96.6
Levofloxacin	50.4	68.6	66.9	63.8	72.7	64.6	68.1	27.2	44.2	31.8	62.7	78.7	64.9	84.5
Meropenem	53.0	82.5	77.1	73.3	84.6	75.2	77.3	25.1	53.3	42.4	80.7	83.5	71.4	83.2
Piperacillin-tazobactam	56.3	73.9	77.6	74.1	82.4	74.8	77.2	39.2	51.9	41.8	77.3	81.7	72.4	85.2

[a] EUCAST (2018).

Table 2 MIC frequency distribution of ceftolozane-tazobactam for *P. aeruginosa* and resistant phenotypes

		Number (cumulative %) at each MIC (mg/L)												
Organism/organism group	Total	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Pseudomonas aeruginosa	6,633	9 (0.2)	33 (0.6)	517 (8.4)	3,317 (58.5)	1,283 (77.8)	503 (85.4)	283 (89.6)	102 (91.2)	63 (92.1)	90 (93.5)	432 (100.0)	0.5	8
Meropenem-nonsusceptible (>2 mg/L)	1,920	0 (0.0)	1 (0.1)	29 (1.6)	346 (19.6)	437 (42.3)	285 (57.2)	178 (66.5)	81 (70.7)	58 (73.7)	87 (78.2)	418 (100.0)	2	>32
Ceftazidime-nonsusceptible (>8 mg/L)	1,713		0 (0.0)	1 (0.1)	43 (2.6)	347 (22.8)	412 (46.9)	257 (61.9)	80 (66.5)	56 (69.8)	87 (74.9)	430 (100.0)	4	>32
Piperacillin-tazobactam-nonsusceptible (>16 mg/L)	1,956		0 (0.0)	7 (0.4)	137 (7.4)	445 (30.1)	427 (51.9)	271 (65.8)	102 (71.0)	61 (74.1)	86 (78.5)	420 (100.0)	2	>32
Cefepime-nonsusceptible (>2 mg/L)	1,493			0 (0.0)	14 (0.9)	207 (14.8)	359 (38.8)	268 (56.8)	88 (62.7)	54 (66.3)	88 (72.2)	415 (100.0)	4	>32
β-lactam-nonsusceptible[a]	1,005			0 (0.0)	2 (0.2)	74 (7.6)	198 (27.3)	158 (43.0)	56 (48.6)	41 (52.6)	80 (60.6)	396 (100.0)	16	>32
MDR	1,827	1 (0.1)	2 (0.2)	9 (0.7)	101 (6.2)	430 (29.7)	387 (50.9)	231 (63.5)	87 (68.3)	60 (71.6)	89 (76.5)	430 (100.0)	2	>32

[a] Nonsusceptible to 4 β-lactams: ceftazidime, cefepime, piperacillin-tazobactam, and meropenem.

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