Activity of Ceftolozane-Tazobactam and Comparators When Tested against Bacterial Surveillance Isolates Collected from Paediatric Patients in Europe during 2012–2017 as Part of a Global Surveillance Program

Dee Shortridge[1]; Leonard R. Duncan[1]; Michael A. Pfaller[1]; Jennifer M. Streit; Robert K. Flamm[1]

JMI Laboratories, North Liberty, Iowa, USA

INTRODUCTION

- Ceftolozane-tazobactam is an antibacterial combination of an antipseudomonal cephalosporin and a well-described β-lactamase inhibitor
  - Ceftolozane-tazobactam has activity against most common β-lactam resistance mechanisms employed by *Pseudomonas aeruginosa*, including AmpC production (PDC), up-regulated efflux pumps, and porin reductions (OprD loss)
  - Ceftolozane-tazobactam also has activity against most ESBL-producing *Enterobacteriaceae* (new taxonomy: Enterobacterales)
- Ceftolozane-tazobactam has been approved in >50 countries, including the US Food and Drug Administration in 2014 and the European Medicines Agency in 2015 to treat complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections in adults
  - Paediatric treatment trials are in progress
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors ceftolozane-tazobactam resistance to gram-negative isolates worldwide
- This study analysed the susceptibility of gram-negative isolates from European paediatric patients

MATERIALS AND METHODS

- A total of 2,136 gram-negative isolates were collected during 2012–2017 from paediatric patients (<18 years old) in 50 European hospitals participating in PACTS
  - Patients ≤1 year old (yo) contributed 43.9% of isolates
  - Other age groups and %: 2-6 yo, 22.0%; 7-12 yo, 18.6%; ≥13 yo, 15.5%
- Isolates were tested for ceftolozane-tazobactam susceptibility (S) by CLSI broth microdilution method at JMI Laboratories using EUCAST breakpoints (2018)
- Other antibiotics tested were amikacin, cefepime, ceftazidime, colistin, levofloxacin, meropenem, and piperacillin-tazobactam
  - Ceftolozane-tazobactam and piperacillin-tazobactam were both tested at a fixed 4 mg/L tazobactam concentration
- Antibiotic-resistant phenotypes identified for *Enterobacteriaceae* (new taxonomy Enterobacterales) included carbapenem-resistant (CRE) and non-CRE extended-spectrum beta-lactamase screen-positive (ESBL, non-CRE)
- Antibiotic-resistant phenotypes identified for *Pseudomonas aeruginosa* included ceftazidime-nonsusceptible, meropenem-nonsusceptible, cefepime-nonsusceptible, piperacillin-tazobactam-nonsusceptible, and nonsusceptible to all 4 β-lactam comparators (β-lactam-nonsusceptible)
- Isolates were considered multidrug-resistant (MDR) if they were nonsusceptible to 3 or more drug classes

RESULTS

- The most common infection type in hospitalised paediatric patients was pneumonia (n=537) followed by bloodstream infection (n=483) and urinary tract infection (n=450), as shown in Figure 1
- The 5 most common species are shown in Figure 2
  - The 3 most common species in each infection type were *Escherichia coli* (n=649), *P. aeruginosa* (n=425), and *Klebsiella pneumoniae* (n=287)
  - The distribution of these 3 species by infection type is shown in Figure 3

Figure 1 Number of isolates per paediatric infection type in European hospitals (PACTS, 2012–2017)

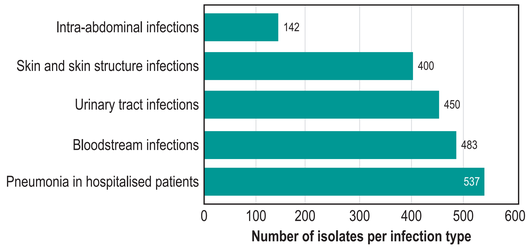
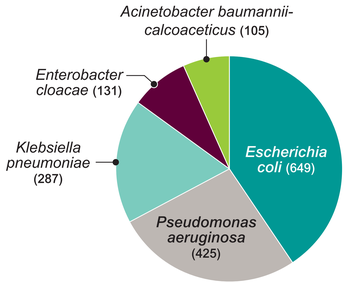


Figure 2 Top 5 pathogens (species and number) isolated from paediatric infections in European hospitals (PACTS 2012–2017)



- *E. coli* was the most frequent isolate from urinary tract and intra-abdominal infections
- *P. aeruginosa* was the most frequent isolate from pneumonia

- Susceptibilities of ceftolozane-tazobactam and comparators for the main species and resistant phenotypes are shown in Table 1
  - For *P. aeruginosa*, ceftolozane-tazobactam (93.2%S) and colistin (98.4%S) were the most active antimicrobials
  - The most active drugs against *Enterobacteriaceae* were meropenem (98.1%S) and amikacin (96.1%S), followed by ceftolozane-tazobactam (89.8%S)
- The ceftolozane-tazobactam MIC distributions for the main pathogens in this study are shown in Table 2

Table 1 Ceftolozane-tazobactam and comparator susceptibility for main pathogen groups and resistant phenotypes (PACTS, 2012–2017)

Organism/organism group	n	% susceptible[a]							
		Ceftolozane-tazobactam	Cefepime	Ceftazidime	Meropenem	Piperacillin-tazobactam	Levofloxacin	Amikacin	Colistin
Enterobacteriaceae	1,417	89.8	77.0	74.8	98.1	83.0	83.1	96.1	85.8
ESBL, non-CRE	271	77.1	10.0	10.3	99.6	58.5	53.7	88.9	97.8
MDR	229	58.1	13.1	16.2	88.2	31.9	35.4	80.8	83.2
Pseudomonas aeruginosa	425	93.2	83.8	80.7	76.9	78.4	71.2	85.2	98.4
MDR	102	73.5	38.2	36.3	16.7	27.5	13.7	48.0	98.0
Meropenem-nonsusceptible	98	72.4	44.9	44.9	0.0	36.7	25.5	55.1	99.0
Ceftazidime-nonsusceptible	82	65.9	24.4	0.0	34.1	8.5	35.4	56.1	98.8
Piperacillin-tazobactam-nonsusceptible	92	68.5	30.4	18.5	32.6	0.0	31.5	55.4	98.9
Cefepime-nonsusceptible	69	59.4	0.0	10.1	21.7	7.2	24.6	43.5	100.0
β-lactam-nonsusceptible	46	45.7	0.0	0.0	0.0	0.0	15.2	34.8	100.0

[a] EUCAST (2018)

Table 2 MIC distribution of ceftolozane-tazobactam for the main pathogens and resistant phenotypes (PACTS, 2012–2017)

Organism/organism group	Total	Ceftolozane-tazobactam MIC mg/L (%)[a]													
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32	MIC_{50}	MIC_{90}
Escherichia coli	649		0 (0.0)	7 (1.1)	262 (41.4)	265 (82.3)	67 (92.6)	29 (97.1)	4 (97.7)	5 (98.5)	2 (98.8)	1 (98.9)	1 (99.1)	6 (100.0)	0.25	0.5
ESBL, non-CRE	141			0 (0.0)	5 (3.5)	39 (31.2)	50 (66.7)	29 (87.2)	3 (89.4)	5 (92.9)	2 (94.3)	1 (95.0)	1 (95.7)	6 (100.0)	0.5	4
Klebsiella pneumoniae	287		0 (0.0)	3 (1.0)	35 (13.2)	99 (47.7)	67 (71.1)	27 (80.5)	10 (84.0)	9 (87.1)	6 (89.2)	4 (90.6)	7 (93.0)	20 (100.0)	0.5	16
ESBL, non-CRE	117				0 (0.0)	17 (14.5)	41 (49.6)	21 (67.5)	9 (75.2)	8 (82.1)	6 (87.2)	4 (90.6)	4 (94.0)	7 (100.0)	1	16
Pseudomonas aeruginosa	425			0 (0.0)	2 (0.5)	24 (6.1)	234 (61.2)	95 (83.5)	21 (88.5)	20 (93.2)	7 (94.8)	5 (96.0)	3 (96.7)	14 (100.0)	0.5	4
Ceftazidime-nonsusceptible	82					0 (0.0)	1 (1.2)	19 (24.4)	15 (42.7)	19 (65.9)	6 (73.2)	5 (79.3)	3 (82.9)	14 (100.0)	4	>32
Piperacillin-tazobactam-nonsusceptible	92				0 (0.0)	1 (1.1)	5 (6.5)	23 (31.5)	16 (48.9)	18 (68.5)	7 (76.1)	5 (81.5)	3 (84.8)	14 (100.0)	4	>32
Cefepime-nonsusceptible	69						0 (0.0)	9 (13.0)	13 (31.9)	19 (59.4)	7 (69.6)	5 (76.8)	3 (81.2)	13 (100.0)	4	>32
Meropenem-nonsusceptible	98					0 (0.0)	22 (22.4)	24 (46.9)	11 (58.2)	14 (72.4)	7 (79.6)	4 (83.7)	3 (86.7)	13 (100.0)	2	>32
β-lactam-nonsusceptible	46						0 (0.0)	5 (10.9)	4 (19.6)	12 (45.7)	6 (58.7)	4 (67.4)	3 (73.9)	12 (100.0)	8	>32
MDR	101					0 (0.0)	12 (11.9)	38 (37.6)	56 (55.4)	74 (73.3)	81 (80.2)	85 (84.2)	88 (87.1)	101 (100.0)	2	>32

[a] EUCAST (2018) susceptible breakpoints shaded

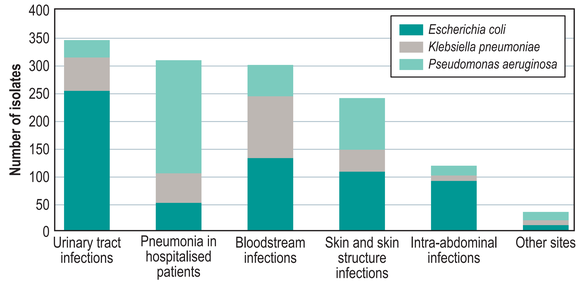
Table 3 Numbers of isolates by patient age for main organism groups

Organism group	≤1 yo	2–6 yo	7–12 yo	>13 yo
All isolates	937 (43.9%)	470 (22.0%)	398 (18.6%)	331 (15.5%)
All *Enterobacteriaceae*	658 (46.4%)	303 (21.4%)	244 (17.2%)	212 (15.0%)
MDR	109 (48.0%)	52 (22.9%)	34 (15.0%)	32 (14.1%)
ESBL, non-CRE	123 (45.4%)	64 (23.6%)	47 (17.3%)	37 (13.7%)
All *P. aeruginosa*	129 (30.4%)	100 (23.5%)	108 (25.4%)	88 (20.7%)
MDR	31 (30.7%)	19 (18.8%)	25 (24.8%)	26 (25.7%)

Abbreviations: yo, year old.

- The number of organisms and organism groups by patient age is shown in Table 3
  - The largest group of patients, ≤1 yo, had the largest number of *Enterobacteriaceae* and *P. aeruginosa* isolates and the largest number of MDR and ESBL, non-CRE

Figure 3 Distribution of 3 most common pathogens for each infection type



CONCLUSIONS

- Ceftolozane-tazobactam susceptibility was 89.8% against *Enterobacteriaceae*, 97.1% against *E. coli*, and 80.5% against *K. pneumoniae* paediatric isolates
  - Meropenem and amikacin were the most active antimicrobials against *Enterobacteriaceae*
- For *P. aeruginosa*, ceftolozane-tazobactam was the most potent β-lactam tested with activity similar to colistin
- Ceftolozane-tazobactam maintained activity against *P. aeruginosa* isolates nonsusceptible to other β-lactams and MDR isolates
- These data suggest that ceftolozane-tazobactam may be a useful treatment for serious paediatric infections caused by gram-negative pathogens, including *P. aeruginosa*

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Contact Information:

Dee Shortridge, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: dee-shortridge@jmilabs.com

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