Activity of Ceftolozane-Tazobactam and Comparators When Tested against Bacterial Surveillance Isolates Collected from Patients at Risk of Infections Caused by Resistant Gram-Negative Pathogens

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Introduction

- Ceftolozane-tazobactam (C-T) is an antipseudomonal cephalosporin combined with a 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 extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae
- C-T has been approved in >60 countries for treatment of complicated urinary tract infections and acute pyelonephritis and for complicated intra-abdominal infections (with metronidazole) in adults
- Hospital-acquired pneumonia, including ventilator-associated pneumonia, clinical treatment trials have recently concluded and regulatory filings are in progress (clinicaltrials.gov Identifier: NCT02070757)
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors C-T resistance worldwide
- The present study analysed gram-negative (GN) pathogen susceptibility (S) in European patients who are considered at risk for infections caused by pathogens resistant to commonly used antimicrobials
  - Patients in the intensive care unit (ICU)
  - Patients on the haematology/oncology or transplant service who may be immunocompromised (IC)
  - Patients >65 years of age (yo)

Materials and Methods

- In 2015-2018, 8,623 GN bacilli, including 6,434 Enterobacteriaceae and 1,497 *Pseudomonas aeruginosa*, were isolated from patient populations described as part of PACTS
- All infection types were included: bloodstream, pneumonia, skin and skin structure, intra-abdominal, and urinary tract
- Isolates were tested for S by the CLSI broth microdilution method, per CLSI M7 (2018), at JMI Laboratories
- In addition to C-T, comparators analysed for this study were cefepime (FEP), levofloxacin (LEV), meropenem (MEM), and piperacillin-tazobactam (PIP-TAZ)
- Enterobacteriaceae screen-positive for ESBL, not resistant to carbapenems (ESBL, non-CRE) was also analysed
- *P. aeruginosa* nonsusceptible to MEM, PIP-TAZ, FEP, or ceftazidime (CAZ) were also analysed
- Interpretive criteria from CLSI M100 (2018) and EUCAST v 8.0 (2018) were used

Results

- The 3 most common GN pathogens for all 3 patient groups were *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa* with some variation between the groups
  - The top 5 species for the 3 groups are shown in Figure 1
  - *P. aeruginosa* was the most common pathogen for ICU patients; *E. coli* was the most common for >65 yo and IC groups
- Figure 2 displays the most common infection types for the 3 groups
  - Pneumonia – ICU group
  - Bloodstream infection – >65 yo and IC groups
- Table 1 shows C-T and comparators %S against Enterobacteriaceae, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* for the 3 groups
  - ICU patients had the lowest %S for *P. aeruginosa* for all drugs tested and the lowest for Enterobacteriaceae for all drugs except levofloxacin
  - The %S for isolates from the IC and >65 yo groups were similar for Enterobacteriaceae
- C-T was the most active agent against *P. aeruginosa*, with ≥90%S for >65 yo and IC groups and >80%S for the ICU group
- C-T susceptibility was >95% for *E. coli* and was second only to MEM, which had >98% susceptibility
- C-T had <75%S against *K. pneumoniae*, and MEM %S ranged from 78.9-85.8 %(EUCAST)
  - Other antimicrobials tested had lower %S against *K. pneumoniae* than C-T or MEM
- Table 2 has the C-T MIC distribution for *P. aeruginosa* and resistant phenotypes for the 3 patient groups
  - C-T activity against isolates nonsusceptible to MEM, FEP and CAZ varied by patient group, with the lowest %S for ICU patients (45.5-63.6%) and the highest for IC patients (70.0-80.0%)
- Table 3 has the C-T MIC distribution for Enterobacteriaceae and ESBL, non-CRE for the 3 patient groups
  - ESBL, non-CRE rates for the 3 groups were: ICU, 20.1%; IC, 17.8%; and >65 yo, 18.3%
  - Activity of C-T against ESBL, nonCRE phenotype isolates varied by patient group, with isolates from ICU patients having the lowest %S (63.6%S) and patients from >65 yo group having the highest %S (77.2%)

Conclusions

- The %S of isolates from patients at risk of infection with gram-negative pathogens was analysed
- Patient groups were: ICU patients, patients >65 yo, and IC patients
- ICU patients had the lowest %S for all antimicrobials tested, suggesting they were more likely to be infected by a resistant pathogen than either the IC or >65 yo group
- MEM and C-T were the most active of the agents against Enterobacteriaceae
- C-T was the most active agent against *P. aeruginosa* for all 3 patient groups

Acknowledgements

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ USA

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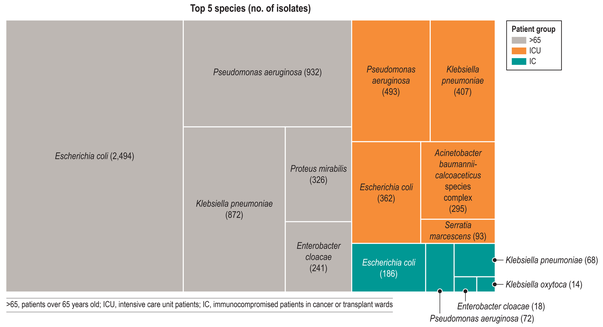
Table 1 Percent susceptible for Enterobacteriaceae and *P. aeruginosa isolates* tested against C-T and comparators from patients in various risk groups

Organisms	%S (CLSI/EUCAST [a]):					
	n	C-T	PIP-TAZ	FEP	MEM	LEV
Enterobacteriaceae ICU	1,283	83.8/80.4	76.5/70.7	73.3/71.4	91.6/92.6	76.6/71.4
Enterobacteriaceae IC	337	92.3/89.3	81.9/75.7	78.6/76.0	95.0/95.5	68.5/64.4
Enterobacteriaceae >65 yo	4,814	91.6/89.3	85.5/80.9	80.0/78.1	96.7/97.2	73.2/68.8
E. coli ICU	362	96.7/95.0	90.1/85.1	77.3/74.9	98.9/98.9	72.7/71.3
E. coli IC	186	99.5/98.9	86.6/81.7	80.6/79.0	100.0/100.0	60.8/57.0
E. coli >65 yo	2,494	98.9/97.8	91.9/87.6	81.5/79.8	99.9/99.9	67.6/99.5
K. pneumoniae ICU	407	64.6/59.2	54.1/46.6	46.2/45.2	75.9/78.9	56.5/49.1
K. pneumoniae IC	68	70.6/61.8	61.8/54.4	57.4/55.9	79.4/82.4	66.2/58.8
K. pneumoniae >65 yo	872	74.2/70.9	65.0/58.2	55.3/54.7	84.5/85.8	64.6/56.8
P. aeruginosa ICU	493	81.9/81.9	57.4/57.4	68.4/68.4	52.5/52.5	61.6/52.8
P. aeruginosa IC	72	95.8/95.8	76.4/76.4	86.1/86.1	79.2/79.2	77.5/67.6
P. aeruginosa >65 yo	932	92.3/92.3	74.0/74.0	81.8/81.8	75.5/75.5	69.7/62.8

[a] CLSI (2018); EUCAST (2018).

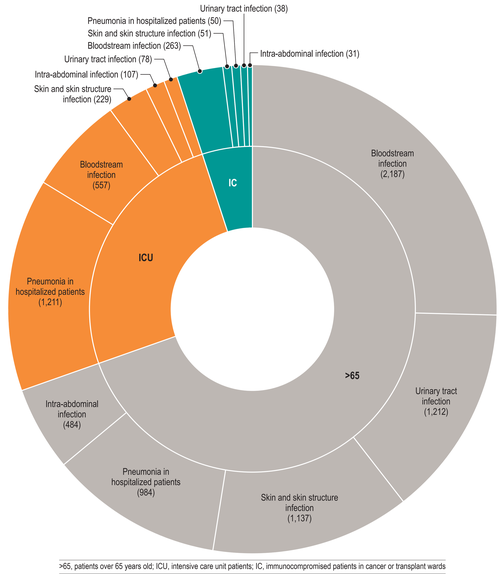
C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; FEP, cefepime; MEM, meropenem; LEV, levofloxacin; ICU, intensive care unit patients; IC, immunocompromised patients in cancer or transplant wards; yo, years old

Figure 1 Top 5 species of isolates by patient group



>65, patients over 65 years old; ICU, intensive care unit patients; IC, immunocompromised patients in cancer or transplant wards

Figure 2 Infection types by patient group



>65, patients over 65 years old; ICU, intensive care unit patients; IC, immunocompromised patients in cancer or transplant wards

Table 2 Antimicrobial activity of ceftolozane-tazobactam tested against *P. aeruginosa* and resistant phenotypes from study patient groups

Patient group Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:											
	≤0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
Intensive care unit patients												
Pseudomonas aeruginosa (493)	2	45	215	97	29	16	8	2	9	70		
	0.4	9.5	53.1	72.8	78.7	81.9	83.6	84	85.8	100	0.5	>32
Meropenem-nonsusceptible (>2 mg/L) (234)	0	7	53	56	21	11	7	2	9	68		
	0	3	25.6	49.6	58.5	63.2	66.2	67.1	70.9	100	2	>32
Ceftazidime-nonsusceptible (>8 mg/L) (177)		0	8	43	26	14	5	2	9	70		
		0	4.5	28.8	43.5	51.4	54.2	55.4	60.5	100	4	>32
Cefepime-nonsusceptible (>2 mg/L) (156)		0	3	31	22	15	4	2	9	70		
		0	1.9	21.8	35.9	45.5	48.1	49.4	55.1	100	32	>32
Piperacillin-tazobactam-nonsusceptible (>16 mg/L) (209)		0	25	55	27	15	8	2	8	69		
		0	12	38.3	51.2	58.4	62.2	63.2	67	100	2	>32
Immunocompromised patients												
Pseudomonas aeruginosa (72)	0	12	39	12	5	1	0	0	0	3		
	0	16.7	70.8	87.5	94.4	95.8	95.8	95.8	95.8	100	0.5	2
Meropenem-nonsusceptible (>2 mg/L) (15)	0	1	2	5	3	1	0	0	0	3		
	0	6.7	20.0	53.3	73.3	80.0	80.0	80.0	80.0	100	1	>32
Ceftazidime-nonsusceptible (>8 mg/L) (15)		0	1	5	5	1	0	0	0	3		
		0	6.7	40.0	73.3	80.0	80.0	80.0	80.0	100	2	>32
Cefepime-nonsusceptible (>2 mg/L) (10)			0	1	5	1	0	0	0	3		
			0	10.0	60.0	70.0	70.0	70.0	70.0	100	2	>32
Piperacillin-tazobactam-nonsusceptible (>16 mg/L) (17)		0	2	6	5	1	0	0	0	3		
		0	11.8	47.1	76.5	82.4	82.4	82.4	82.4	100	2	>32
Patients >65 years old												
Pseudomonas aeruginosa (932)	10	120	483	191	45	11	7	12	16	37		
	1.2	13.9	65.8	86.3	91.1	92.3	93.0	94.3	96.0	100	0.5	2
Meropenem-nonsusceptible (>2 mg/L) (228)	0	3	42	82	25	7	5	11	16	37		
	0	1.3	19.7	55.7	66.7	69.7	71.9	76.8	83.8	100	1	>32
Ceftazidime-nonsusceptible (>8 mg/L) (203)	0	1	12	71	43	9	3	11	16	37		
	0	0.5	6.4	41.4	62.6	67.0	68.5	73.9	81.8	100	2	>32
Cefepime-nonsusceptible (>2 mg/L) (170)		0	4	51	36	11	7	9	16	36		
		0	2.4	32.4	53.5	60.0	64.1	69.4	78.8	100	2	>32
Piperacillin-tazobactam-nonsusceptible (>16 mg/L) (241)	0	1	27	86	45	11	7	12	16	36		
	0	0.4	11.6	47.3	66.0	70.5	73.4	78.4	85.1	100	2	>32

[a] Criteria as published by EUCAST 2018; susceptible breakpoint column is shaded.

Table 3 Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and resistant phenotypes from study patient groups

Patient group Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:											
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
ICU patients													
Enterobacteriaceae (1,283)	10	319	389	224	90	43	41	32	21	16	98		
	0.8	25.6	56	73.4	80.4	83.8	87	89.5	91.1	92.4	100	0.25	16
ESBL, non-CRE (258)	0	7	55	63	39	27	25	11	9	6	16		
	0	2.7	24	48.4	63.6	74.0	83.7	88.0	91.5	93.8	100	1	16
IC patients													
Enterobacteriaceae (337)	5	112	122	42	20	10	6	4	3	1	12		
	1.5	34.7	70.9	83.4	89.3	92.3	94.1	95.3	96.1	96.4	100	0.25	2
ESBL, non-CRE (60)	1	5	12	15	11	7	5	0	2	1	1		
	1.7	10.0	30.0	55.0	73.3	85.0	93.3	93.3	96.7	98.3	100	0.5	4
Patients >65 yo													
Enterobacteriaceae (4,814)	96	1,578	1,687	702	233	115	87	60	50	40	166		
	2	34.8	69.8	84.4	89.2	91.6	93.4	94.7	95.7	96.6	100	0.25	2
ESBL, non-CRE (880)	2	68	251	221	137	68	48	20	20	14	31		
	0.2	8.0	36.5	61.6	77.2	84.9	90.3	92.6	94.9	96.5	100	0.5	4

[a] Criteria as published by EUCAST 2018; susceptible breakpoint column is shaded.

ESBL, extended-spectrum β-lactamase; CRE, carbapenemase-resistant Enterobacteriaceae; ICU, intensive care unit patients; IC, immunocompromised patients in cancer or transplant wards; yo, years old.

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