Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2012–2016) *Enterobacteriaceae* and *Pseudomonas aeruginosa* from ICU vs Non-ICU Respiratory Isolates Collected in US Medical Centers

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INTRODUCTION

- Ceftolozane-tazobactam (C-T) is a combination of a novel antipseudomonal cephalosporin and a well-described β-lactamase inhibitor
- C-T was approved by the United States (US) Food and Drug Administration in 2014 for complicated urinary tract infections, including acute pyelonephritis, and complicated intra-abdominal infections, used in combination with metronidazole
- C-T is currently in clinical trials for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors C-T resistance to gram-negative (GN) isolates worldwide
- This study examined the activities of C-T and comparators against GN respiratory isolates from patients hospitalized with pneumonia in an intensive care unit (ICU) and in a non-ICU setting

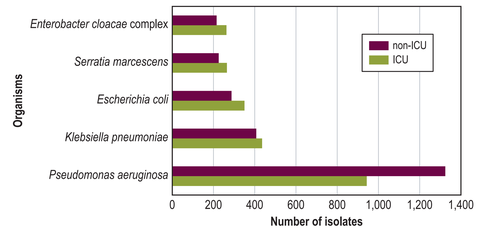
MATERIALS AND METHODS

- A total of 6,371 GN isolates were collected from respiratory tract cultures in patients hospitalized with pneumonia (PHP) at 30 US medical centers from 2012–2016
- 3,100 isolates were from ICU patients, and 3,271 isolates were from non-ICU patients
  - Isolates from patients without ICU/non-ICU information were excluded
- Isolates were tested for susceptibility (S) to C-T and comparators by CLSI broth microdilution methodology at JMI Laboratories
  - Other antibiotics tested included amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), meropenem (MER), and piperacillin-tazobactam (TZP)
  - CLSI (2017) interpretive criteria were used for all antibiotics except COL with *Enterobacteriaceae* (ENT), for which EUCAST (2017) criteria were used
    - CLSI (2017) C-T breakpoints for ENT are ≤2.0 mg/L for S, 4.0 mg/L for intermediate (I), and ≥8.0 mg/L for resistant (R); *P. aeruginosa* C-T breakpoints are ≤4.0 mg/L for S, 8.0 mg/L for I, and ≥16.0 mg/L for R

RESULTS

- The 5 most common species for ICU vs. non-ICU PHP are shown in Figure 1
  - The most common organism isolated from respiratory cultures was *Pseudomonas aeruginosa* (PSA) for ICU (30.5%) and non-ICU (40.5%)
  - The 4 most common ENT species for ICU and non-ICU patients were *Klebsiella pneumoniae* (KPN), *Escherichia coli* (EC), *Serratia marcescens* (SM), and *Enterobacter cloacae* complex (ECC)
    - These 4 species accounted for 42% and 35% of isolates from PHP for ICU and non-ICU, respectively
- ICU ENT isolates generally had a slightly lower %S for most of the drugs compared to non-ICU (Table 1)
  - Agents with %S at 90% or higher for both groups were AMK, C-T, and MER
  - KPN isolates showed the greatest difference between ICU and non-ICU origin with a lower %S in ICU isolates
  - EC isolates had very similar %S between groups with <2% difference
- Susceptibilities of PSA were similar for both groups with ≤3% difference (Table 1)
  - C-T was the most active beta-lactam with %S similar to AMK and COL

Figure 1. Five most common gram-negative species in ICU and non-ICU patients hospitalized with pneumonia



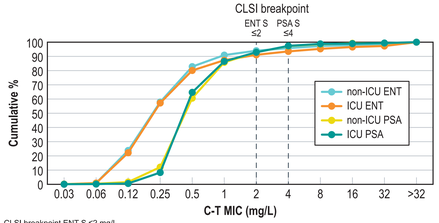
- For C-T, activity against isolates from ICU vs. non-ICU was similar (Table 1, Figures 2 and 3)
  - The %S of PSA to C-T was 97% for ICU and non-ICU patients
  - The %S of ENT to C-T was slightly higher for non-ICU, 94% vs. 91% for ICU patients
  - The %S and cumulative % MIC distribution of EC and KPN for C-T are shown in Table 1 and Figure 3
    - For EC, C-T %S was similar for both groups with 97.7%S for ICU and 99.3% for non-ICU
    - For KPN, C-T %S was higher in the non-ICU (93.6%) group than the ICU group (87.4%), which was the largest difference between groups

Table 1. Percent susceptibility to C-T and comparators for the 5 top GN species from patients hospitalized with pneumonia in the ICU and non-ICU

		% Susceptible†						
Organism	Number	C-T	AMK	FEP	CAZ	COL‡	MER	TZP
ENT ICU§	1,802	91.1	98.5	89.7	84.7	75.8	96.6	86.9
ENT non-ICU□	1,578	94.0	98.7	91.8	87.8	73.7	98.4	89.5
EC ICU	350	97.7	99.4	85.7	86.9	100.0	99.7	91.1
EC non-ICU	287	99.3	99.6	85.7	87.5	99.3	100.0	90.5
KPN ICU	435	87.4	94.7	83.0	81.8	97.0	90.6	83.4
KPN non-ICU	407	93.6	96.3	87.7	86.0	98.3	96.3	88.9
SM ICU	265	97.7	100.0	96.6	97.0	N/A	98.9	94.3
SM non-ICU	225	97.3	98.7	97.3	97.8	N/A	97.3	92.0
ECC ICU	263	80.2	99.6	87.8	71.1	78.5	96.2	79.8
ECC non-ICU	216	81.0	100.0	91.7	73.1	80.3	99.5	80.0
PSA ICU	944	97.4	98.2	84.9	83.4	99.3	78.6	78.8
PSA non-ICU	1,324	97.3	95.2	84.6	84.0	99.5	80.9	78.5

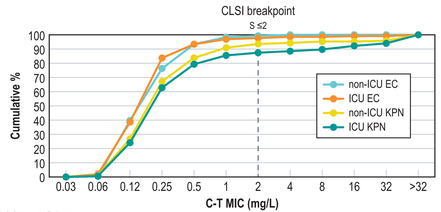
† CLSI 2017
‡ EUCAST 2017 used for *Enterobacteriaceae*
§ Organisms include: *Citrobacter braakii* (2), *C. freundii* (17), *C. freundii* species complex (8), *C. koseri* (31), *C. sedlakii* (1), *Enterobacter aerogenes* (153), *E. amnigenus* (1), *E. asburiae* (11), *E. cancerogenus* (1), *E. cloacae* (185), *E. cloacae* species complex (79), *E. kobei* (1), *E. taylorae* (1), *Escherichia coli* (350), *Hafnia alvei* (3), *Klebsiella oxytoca* (160), *K. pneumoniae* (435), *K. variicola* (2), *Morganella morganii* (15), *Pantoea agglomerans* (2), *P. dispersa* (1), *Pluralibacter gergoviae* (1), *Proteus mirabilis* (52), *Providencia rettgeri* (4), *P. stuartii* (8), *Raoultella ornithinolytica* (3), *R. planticola* (1), *Serratia liquefaciens* (4), *S. marcescens* (265), *S. odorifera* (1), *S. plymuthica* (1), *S. rubidaea* (1), unspecified *Citrobacter* (2), unspecified *Raoultella* (1)
□ Organisms include: *Citrobacter braakii* (3), *C. freundii* (25), *C. freundii* species complex (5), *C. koseri* (35), *C. sedlakii* (1), *Cronobacter sakazakii* (3), *Enterobacter aerogenes* (105), *E. amnigenus* (1), *E. cloacae* (181), *E. cloacae* species complex (35), *Escherichia coli* (287), *Ewingella americana* (1), *Hafnia alvei* (2), *Klebsiella oxytoca* (103), *K. pneumoniae* (407), *K. variicola* (1), *Kluyvera ascorbata*(1), *Kosakonia cowanii* (1), *Morganella morganii* (20), *Pantoea agglomerans* (1), *Pluralibacter gergoviae* (1), *Proteus mirabilis* (89), *P. vulgaris* (2), *Providencia rettgeri* (9), *P. stuartii* (18), *Rahnella aquatilis* (1), *Raoultella ornithinolytica* (2), *Serratia liquefaciens* (7), *S. marcescens* (225), *S. rubidaea* (1), unspecified *Cedecea* (1), unspecified *Pantoea* (2), unspecified *Raoultella* (1), unspecified *Serratia* (1)

Figure 2. Cumulative percent MIC distribution of C-T for *Enterobacteriaceae* (ENT) and *P. aeruginosa* (PSA) in ICU and non-ICU patients



CLSI breakpoint ENT S ≤2 mg/L
CLSI breakpoint PSA S ≤4 mg/L

Figure 3. Cumulative percent MIC distribution of C-T for *E. coli* (EC) and *K. pneumoniae* (KPN) in ICU and non-ICU patients



CLSI breakpoint S ≤2 mg/L

CONCLUSIONS

- The most common gram-negative pathogen isolated from PHP was PSA
  - PSA was isolated from 30.5% of ICU respiratory cultures and from 40.5% of non-ICU patients
  - KPN and EC combined were isolated from 25.3% of ICU and 21.2% of non-ICU PHP
- For ENT overall susceptibility, AMK, MER, and C-T were the most active
  - MER and C-T had slightly higher %S for non-ICU ENT compared to ICU, while AMK %S was similar for both groups
- For PSA from ICU and non-ICU, C-T, AMK, and COL were extremely active with >95%S
  - C-T was the most active beta-lactam
- C-T showed potent activity against ICU and non-ICU isolates for ENT and PSA
- These data suggest that C-T may be a valuable treatment option for pneumonia caused by the most common gram-negative pathogens in ICU and non-ICU patients

Acknowledgements

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