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# Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2014-2016) *P. aeruginosa* Isolates from Hospitalized Patients with Bloodstream Infections and Pneumonia in European Medical Centres

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http://tinyurl.com/jrymrjs

## Amended Abstract

**Background:** Ceftolozane-tazobactam (C-T) is an antibacterial combination consisting of a novel antipseudomonal cephalosporin and a well-established β-lactamase inhibitor that inhibits most Ambler class A and some class C enzymes. C-T was approved by the US Food and Drug Administration in 2014 and by the European Medicine Agency in 2015 for complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections. The Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS) is a global surveillance program that monitors gram-negative isolate resistance to C-T. Data from PACTS for *Pseudomonas aeruginosa* (PSA) isolates collected from bloodstream infections (BSI) and pneumonia in hospitalized patients (PHP) from 2014-2016 were analysed for this study.

**Methods and Materials:** A total of 2,006 PSA isolates (550 BSI, 1,456 PHP) were collected from 42 European hospitals and tested for susceptibility to C-T in a central monitoring laboratory (JMI Laboratories) that followed CLSI broth microdilution methodology. Other antibiotics tested were amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LVX), meropenem (MER), and piperacillin-tazobactam (TZP). The following resistant phenotypes were analysed: ceftazidime nonsusceptible (CAZ-NS); meropenem nonsusceptible (MER-NS); multidrug-resistant (MDR); extensively drug-resistant (XDR); and beta-lactam NS (BL-NS) to MER, CAZ, FEP, and TZP. EUCAST (2017) interpretive criteria were used.

**Results:** For BSI isolates, 90.7% were susceptible (S) to C-T at ≤4 mg/L, 87.1% were S to AMK, 82.4%S to FEP, 77.8%S to CAZ, 98.5%S to COL, 68.4%S to LVX, 76.7%S to MER, and 76.8%S to TZP. For PHP isolates, C-T inhibited 89.3% at ≤4 mg/L, 80.7% were S to AMK, 76.4%S to FEP, 71.8%S to CAZ, 99.5%S to COL, 58.1%S to LVX, 67.9%S to MER, and 63.8%S to TZP. PHP isolates were more resistant than BSI isolates and had a higher percentage of the resistant phenotypes characterized in this study, including higher rates of MDR (35.9% of PHP vs. 24.7% of BSI) and XDR (22.5% of PHP vs. 16.0% of BSI). COL was the most active antibiotic inhibiting all but 8 PHP and 8 BSI isolates.

**Conclusions:** C-T demonstrated potent activity against BSI and PHP PSA isolated from patients in European hospitals. PHP isolates were more resistant to all drugs tested compared to BSI isolates. For BSI and PHP PSA, including MDR isolates, C-T was more active than all comparators except COL.

| | | % Susceptible[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PSA | N (%) | C/T | FEP | CAZ | MER | TZP | LVX | AMK | COL |
| BSI | 550 | 90.7 | 82.4 | 77.8 | 76.7 | 76.8 | 68.4 | 87.1 | 98.5 |
| MDR | 136 (24.7) | 62.5 | 33.8 | 25.0 | 25.0 | 18.4 | 7.4 | 50.0 | 98.5 |
| XDR | 88 (16.0) | 45.5 | 20.5 | 12.5 | 8.0 | 5.7 | 1.1 | 34.1 | 97.7 |
| CAZ-NS | 122 (22.2) | 60.7 | 29.5 | 0.0 | 36.1 | 10.7 | 22.1 | 54.1 | 98.4 |
| MER-NS | 128 (23.3) | 61.7 | 43.8 | 39.1 | 0.0 | 34.4 | 25.8 | 54.7 | 98.4 |
| TZP-NS | 127 (23.1) | 62.2 | 28.3 | 14.2 | 33.9 | 0.0 | 17.3 | 52.0 | 100.0 |
| BL-NS | 58 (10.5) | 32.8 | 0.0 | 0.0 | 0.0 | 0.0 | 6.9 | 27.6 | 100.0 |
| PHP | 1,456 | 89.3 | 76.4 | 71.8 | 67.9 | 68.3 | 58.1 | 80.7 | 99.5 |
| MDR | 522 (35.9) | 70.9 | 38.7 | 32.6 | 20.5 | 23.2 | 10.2 | 51.1 | 99.0 |
| XDR | 327 (22.5) | 54.1 | 16.8 | 12.2 | 8.3 | 4.3 | 2.1 | 33.0 | 98.5 |
| CAZ-NS | 411 (28.2) | 63.5 | 26.5 | 0.0 | 29.9 | 8.8 | 21.7 | 52.3 | 98.8 |
| MER-NS | 467 (32.1) | 67.9 | 41.8 | 38.3 | 0.0 | 29.3 | 18.8 | 51.4 | 99.1 |
| TZP-NS | 459 (31.5) | 66.4 | 29.4 | 18.3 | 28.1 | 0.0 | 19.6 | 52.9 | 99.1 |
| BL-NS | 241 (16.6) | 41.5 | 0.0 | 0.0 | 0.0 | 0.0 | 5.8 | 29.5 | 99.2 |

[a] EUCAST (2017)

## Introduction

- Ceftolozane/tazobactam (C-T) is an antibacterial combination consisting of a novel antipseudomonal cephalosporin and a well-established β-lactamase inhibitor that inhibits most Ambler class A and some class C enzymes
- C-T was approved by the US Food and Drug Administration in 2014 and by the European Medicine Agency in 2015 for complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections (1.5 g [1 g C + 0.5 g T] q8h)
  - Also approved in Canada, Switzerland, Australia, and New Zealand for the same indications and dosage
- C-T is currently in Phase 3 clinical trials for treatment of hospital associated bacterial pneumonia and ventilator associated pneumonia (3 g [2 g C + 1 g T] q8h)
- The Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS) is a global surveillance program that monitors resistance of gram-negative isolates to C-T
  - Data from PACTS for *Pseudomonas aeruginosa* (PSA) isolates collected from bloodstream infections (BSI) and pneumonia in hospitalized patients (PHP) in 42 European hospitals from 2014-2016 were analysed for this study

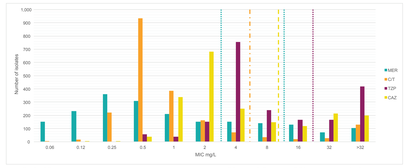
## Materials and Methods

- A total of 2,006 PSA isolates (550 BSI, 1,456 PHP) were collected from 42 European hospitals in 23 countries
- C-T and comparator antibiotics were tested for susceptibility by CLSI broth microdilution methodology in the central monitoring laboratory, JMI Laboratories
- Comparators tested were amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LVX), meropenem (MER), and piperacillin/tazobactam (TZP)
- Resistant phenotypes analysed according to EUCAST (2016) interpretive criteria included ceftazidime nonsusceptible (CAZ-NS); meropenem NS (MER-NS); piperacillin-tazobactam NS (TZP-NS); multidrug-resistant (MDR); extensively drug-resistant (XDR); and beta-lactam NS (BL-NS) to MER, CAZ, FEP, and TZP
- Classifications for MDR and XDR were based on the following recommended parameters:
  - MDR = nonsusceptible (NS; CLSI/EUCAST breakpoints) to at least 3 antimicrobial classes
  - XDR = susceptible (S) to 2 or fewer antimicrobial classes (Magiorakos et al., 2012)
- EUCAST (2017) C-T interpretive criteria for *P. aeruginosa* are ≤4 mg/L S and >4mg/L R

## Results

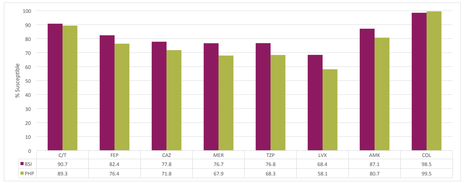
- MIC distributions of the combined PSA isolates (N=2,006) for C-T, MER, CAZ, and TZP are shown in Figure 1
  - C-T was more active than comparators TZP, CAZ, and MER against all PSA
  - C-T $MIC_{50/90}$ 0.5/8 mg/L, 89.7%S; MER $MIC_{50/90}$ 0.5/16 mg/L, 70.3%S; TZP $MIC_{50/90}$ 4/>32 mg/L, 70.7%S; and CAZ $MIC_{50/90}$ 2/32 mg/L, 73.4%S
- BSI isolates (n=550) were 90.7% susceptible (S) to C-T at ≤4 mg/L, 87.1%S to AMK, 82.4%S to FEP, 77.8%S to CAZ, 98.5%S to COL, 68.4%S to LVX, 76.7%S to MER, and 76.8%S to TZP (Figure 2)

**Figure 1 MIC distributions of all PSA isolates for C-T, MER, TZP, and CAZ (n=2,006, PACTS 2014-2016)**




Key: EUCAST breakpoints are indicated with dashed vertical lines: MER teal, C-T orange,TZP purple, and CAZ yellow

**Figure 2 Susceptibilities of C-T and comparators vs. BSI (n=550) and PHP (n=1,456) *P. aeruginosa* isolates (PACTS, 2014–2016)**




- PHP isolates (n=1,456) were 89.3%S to C-T at ≤4 mg/L, 80.7%S to AMK, 76.4%S to FEP, 71.8%S to CAZ, 99.5%S to COL, 58.1%S to LVX, 67.9%S to MER, and 68.3%S to TZP (Figure 2)
- C-T was more active than other beta-lactam antibiotics against isolates with resistant phenotypes (Figures 3 and 4)
  - The resistant phenotypes (n, %) analysed for this study are shown in the abstract table, by infection type
  - 58 BSI isolates were NS to all other beta-lactams (FEP, CAZ, MER, and TZP) and 32.8% were S to C-T (Figure 3)
  - 241 PHP isolates were NS to all other beta-lactams and 41.5% were S to C-T (Figure 4)

## Conclusions

- C-T demonstrated potent activity against BSI and PHP PSA isolates from patients in European hospitals
  - PHP isolates were more resistant to all drugs tested compared to BSI isolates
- C-T retained activity against PSA isolates that were nonsusceptible to the comparator beta-lactams in this study
- C-T was more active than all comparators except COL against BSI and PHP PSA, including MDR and XDR isolates

## Acknowledgements

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**Figure 3 Susceptibilities of C-T and beta-lactam comparators against BSI isolates with various resistant phenotypes, including BL-NS**

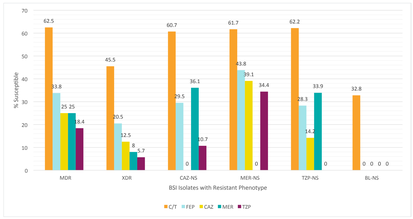
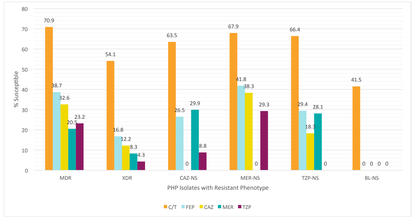



**Figure 4 Susceptibilities of C-T and beta-lactam comparators against PHP isolates with various resistant phenotypes, including BL-NS**

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