Activity of Ceftolozane/Tazobactam and Comparators against Clinical MDR and DTR *Pseudomonas aeruginosa* Isolates – SMART United States 2018-2020

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Introduction

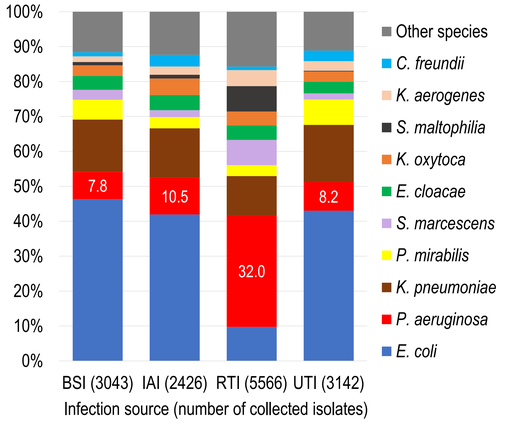
Antimicrobial resistance of *P. aeruginosa* to commonly used β-lactams is typically higher in isolates collected from ICU patients and those with hospital-acquired infections. *P. aeruginosa* with multidrug-resistance (MDR) or difficult-to-treat resistance (DTR) is especially challenging as clinicians have limited treatment options. Ceftolozane/tazobactam was specifically developed to provide enhanced antibacterial activity against *P. aeruginosa*. We evaluated the activity of ceftolozane/tazobactam (C/T) and comparators against clinical *P. aeruginosa* isolates by ward type and length of hospital stay at time of specimen collection, including against MDR and DTR isolates.

Methods

In 2018-2020, 24 clinical labs participated in the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program in the United States, and each collected up to 250 consecutive gram-negative pathogens per year from patients with bloodstream, intraabdominal, lower respiratory tract, and urinary tract infections. MICs were determined using CLSI broth microdilution and interpreted with CLSI 2022 breakpoints [1, 2].

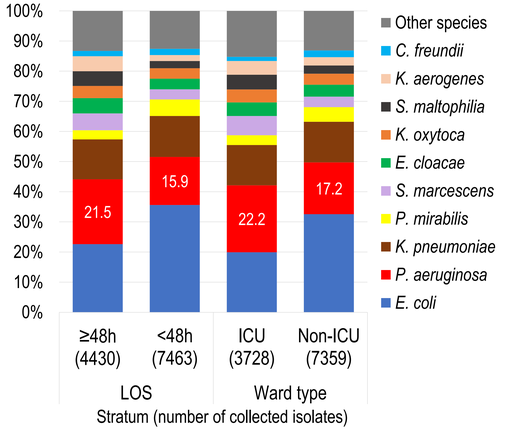
Multidrug-resistant (MDR) phenotype was defined as resistant (R) to ≥3 sentinel drugs: amikacin, aztreonam, cefepime, colistin, imipenem, levofloxacin, and piperacillin/tazobactam; difficult-to-treat resistance (DTR) was defined as nonsusceptibility [I or R] to all tested β-lactams excluding ceftolozane/tazobactam (aztreonam, cefepime, ceftazidime, cefoxitin, ceftriaxone, ertapenem [latter three for Enterobacterales only], imipenem, meropenem, piperacillin/tazobactam) and fluoroquinolones (ciprofloxacin [tested in 2018 only], levofloxacin).

Figure 1. Species distribution (ranked by prevalence among all collected isolates) and proportion of *P. aeruginosa*, stratified by infection source



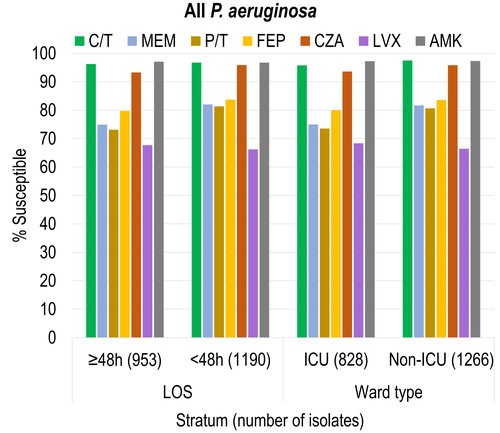
BSI, bloodstream infection; IAI, intraabdominal infection; RTI, lower respiratory tract infection; UTI, urinary tract infection

Figure 2. Species distribution (ranked by prevalence among all collected isolates) and proportion of *P. aeruginosa*, stratified by length of stay (LOS) at time of specimen collection and by ward type



Results

Figure 3. Susceptibility of all collected *P. aeruginosa* isolates, stratified by length of stay (LOS) at time of specimen collection and ward type



C/T, ceftolozane/tazobactam; MEM, meropenem; P/T, piperacillin/tazobactam; FEP, cefepime; CZA, ceftazidime/avibactam; LVX, levofloxacin; AMK, amikacin.

Figure 4. Proportion of MDR and DTR isolates among collected *P. aeruginosa*, stratified by length of stay (LOS) at time of specimen collection and ward type

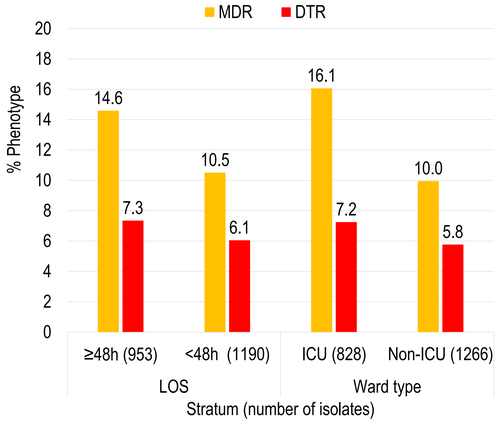
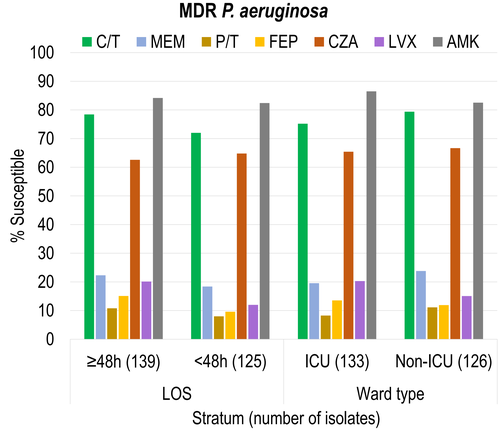
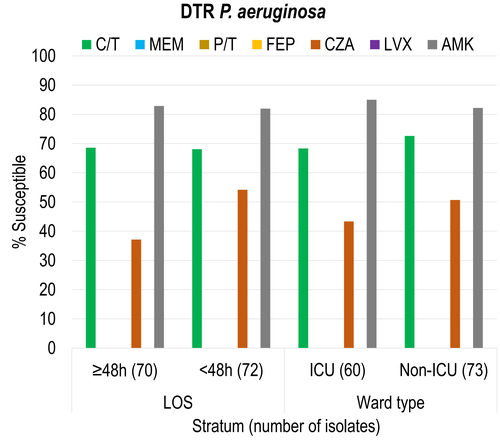


Figure 5. Susceptibility of MDR *P. aeruginosa* isolates, stratified by length of stay (LOS) at time of specimen collection and ward type



C/T, ceftolozane/tazobactam; MEM, meropenem; P/T, piperacillin/tazobactam; FEP, cefepime; CZA, ceftazidime/avibactam; LVX, levofloxacin; AMK, amikacin.

Figure 6. Susceptibility of DTR *P. aeruginosa* isolates, stratified by length of stay (LOS) at time of specimen collection and ward type



C/T, ceftolozane/tazobactam; MEM, meropenem; P/T, piperacillin/tazobactam; FEP, cefepime; CZA, ceftazidime/avibactam; LVX, levofloxacin; AMK, amikacin.

Results Summary

- *P. aeruginosa* was the most common species (32%) among consecutively collected gram-negative pathogens from patients with RTI, compared to 8-11% among isolates from patients with BSI, IAI, and UTI (Figure 1).
- *P. aeruginosa* was more commonly collected from patients with length of stay ≥48 hours and patients in ICUs (Figure 2).
- C/T and amikacin were the only studied agents with activity >95% against all isolates in all strata, with only small differences between the strata. Susceptibility to commonly used β-lactams was 4-8 percentage points lower among isolates collected ≥48h post-admission than <48h and from patients in ICUs compared to non-ICU wards (Figure 3).
- Correspondingly, the prevalence of MDR and DTR isolates was higher among isolates collected ≥48h post-admission than <48h and those collected from ICU patients than non-ICU (Figure 4).
- When the susceptibility of the MDR and DTR subsets was analyzed, the differences between the strata were less clear (Figures 5 and 6). C/T remained the β-lactam with the highest percent susceptible in each stratum and was active against ≥72% of MDR and ≥68% of DTR isolates, 7-31 percentage points higher than ceftazidime/avibactam.

Conclusions

Based on these *in vitro* data, C/T represents a treatment option for patients in the United States with infections caused by MDR and DTR *P. aeruginosa*, regardless of time to infection or treatment in the ICU.

References:

1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eleventh Edition.* CLSI document M07-Ed11. 2018. CLSI, Wayne, PA.
2. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing – 32nd ed.* CLSI Supplement M100. 2022. CLSI, Wayne, PA.

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