Activity of anti-pseudomonal antibiotics among all Pseudomonas aeruginosa (PSA) at an academic medical health system, including β-lactam, multi-drug (MDR) and extensively drug resistant (XDR) strains

Warren Rose[1], Benjamin Heikkinen[1], Janet Raddatz[2], Laura Puzniak[2], Ryan Dillon[2], Lucas Schulz[3]
[1]University of Wisconsin-Madison [2]Merck & Co., Inc., Kenilworth, NJ, USA [3] UW Health, Madison WI

School of Pharmacy
UNIVERSITY OF WISCONSIN–MADISON

UWHealth

Background

- *Pseudomonas aeruginosa (*PSA) with multidrug resistant (MDR) and extensive drug resistance (XDR) are a growing threat, and appropriate initial treatment is critical.
- Comprehensive susceptibility analyses of newer agents among PSA clinical isolates in comparison with other anti-PSA antibiotics remain limited; this is in part due to the absence of routine susceptibility testing of newer antibacterials.
- Recently, PSA has been categorized as **"difficult-to-treat"**, defined as non-susceptibility to all of the following: piperacillin/ tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.
- C/T is a novel antibiotic with broad gram-negative *in vitro* susceptibility among surveillance studies. Recently, C/T was included in recommendations for difficult-to-treat PSA (Table 1)[1]

Table 1: C/T as one of the preferred treatment options assuming antibiotic susceptibility

Source of Infection	C/T as a preferred option
Cystitis	☑
Pyelonephritis or cUTI	☑
Infections outside of the urinary tract	☑

- The objective of this study was to evaluate CT susceptibility and other anti-PSA agents among isolates with MDR, XDR and pan-β-lactam resistance.

Methods

- This retrospective, cohort analysis of all positive PSA cultures collected from adult patients between April 2016 and December 2018 (32 months) at a 505-bed academic health system, UW Health, in Madison, WI, USA.
- Non-Pseudomonas aeruginosa isolates and mucoid strains were excluded
- Antimicrobial susceptibility was prospectively performed using Kirby Bower disk diffusion and interpreted by BIOMIC V3 during routine clinical care.
- For all PSA cultures, initial susceptibility testing included: C/T, amikacin (AMK), aztreonam (ATM), cefepime (FEP), ciprofloxacin (CIP), doripenem (DOR), gentamicin (GEN), imipenem (IPM), meropenem (MER), piperacillin/ tazobactam (TZP), and tobramycin (TOB) were reported
- **MDR**, **XDR** and pan-β-lactam resistance (**PBLR**) were also categorized using standard definitions and reported without regard to duplication.[2]

Results

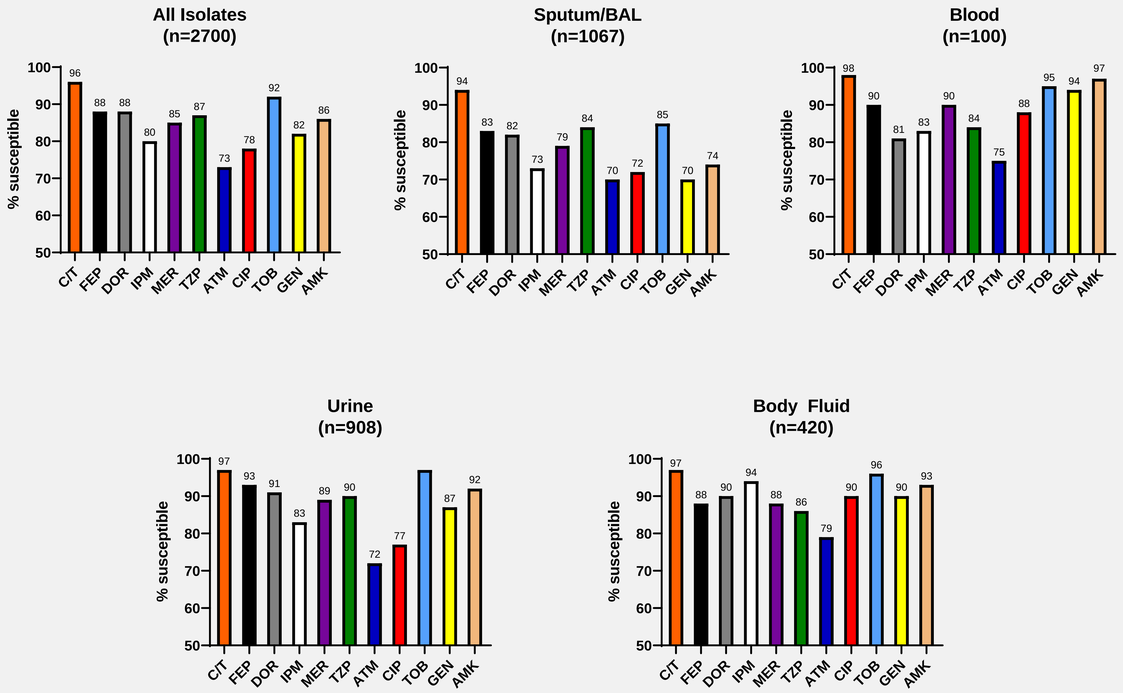
- A total of 2,702 PSA isolates from 2,586 cultures in 1,306 individual patients were collected. Most isolates were from the lung 1069/2702 (40%), followed by urine 908/2702 (34%), and body fluids 420/2702 (16%).
- C/T had the greatest percent susceptibility across all culture locations (96%)
- Of 2634 isolates tested for C/T susceptibility, only 56 (2%) were resistant
- All (n=100) PSA blood cultures were susceptible to C/T (100%)

- In MDR/XDR PSA isolates C/T and TOB retained the greatest susceptibility **(Fig 2)**
  - C/T susceptibility: 69% (MDR) and 55% (XDR)
  - TOB susceptibility: 45% (MDR) and 34% (XDR)

- For PBLR strains C/T retained the greatest susceptibility rate with a median MIC of 8 µg/mL.

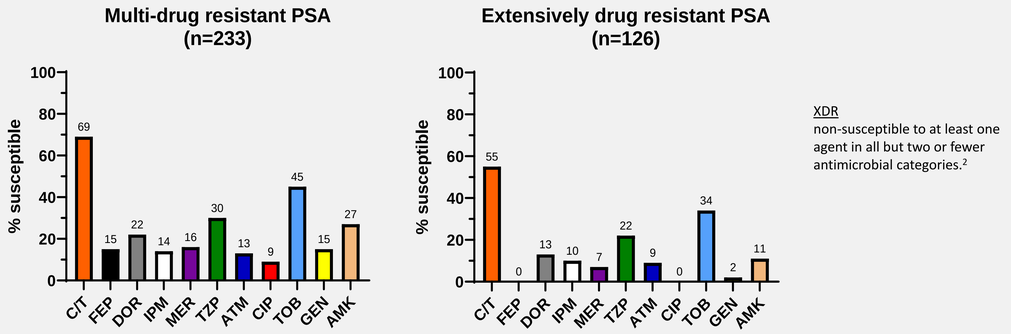
Results

Figure 1. Susceptibility rates by antibiotic categorized by culture site. *DOR was not tested in all isolates: Total number of isolates tested was 2700, 1067, 100, 908, and 420 for overall, sputum/BAL, blood, urine, body fluid, respectively.



Ceftolozane/tazobactam (C/T), amikacin (AMK), aztreonam (ATM), cefepime (FEP), ciprofloxacin (CIP), doripenem (DOR), gentamicin (GEN), imipenem (IPM), meropenem (MER), piperacillin/ tazobactam (TZP), and tobramycin (TOB)

Figure 2. Susceptibility rates among MDR/XDR PSA. *DOR was not tested in all isolates: Total number of isolates tested was 233 MDR and 126 XDR.



MDR
non-susceptibility ≥ 3 classes: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems.[2]

XDR
non-susceptible to at least one agent in all but two or fewer antimicrobial categories.[2]

Abbr: Ceftolozane/tazobactam (C/T), amikacin (AMK), aztreonam (ATM), cefepime (FEP), ciprofloxacin (CIP), doripenem (DOR), gentamicin (GEN), imipenem (IPM), meropenem (MER), piperacillin/ tazobactam (TZP), and tobramycin (TOB)

Results

Table 2. Susceptibility rates in Pan β-lactam resistant (PBLR) strains (n=70)

Agent	PBLR PSA (n,%)
Ceftolozane/tazobactam	39/70 (56%)
Ciprofloxacin	33/70 (47%)
Tobramycin	36/70 (51%)
Gentamicin	29/70 (41%)
Amikacin	30/70 (43%)

70 unique isolates from 66 unique patients with non-resistant AST results. 2 isolates were isolated from the same culture specimen

Conclusions

- Routine susceptibility testing of C/T against PSA at an academic medical center demonstrated high susceptibility.
  - Over a 2.5-year period C/T susceptibility was 96% among PSA from all sites and 2% resistant
  - The number of resistant C/T isolates increased each year of the study
- C/T showed the highest susceptibility among all anti-PSA antibiotics for all culture locations and for MDR and XDR isolates.
- Among the Sputum/BAL isolates C/T was the only antibiotic with >90% susceptibility and one of five antibiotics with >80% susceptibility.
- Only C/T retained over 50% susceptibility in PBLR PSA strains
- Given the high susceptibility of C/T in this study, it is a reliable option for PSA
- Given the high rates of resistance to traditional anti-PSA agents and the difficulty to treat PSA infections, the value of new agents with high rates of in vitro susceptibility in the gram-negative armamentarium is high.

References
1. IDSA Guidelines
2. Magiorakos et. al., Clin Microbiol Infect 2012:18(3):268-81.

Acknowledgements: This work was funded, in part, by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

IDWeek Advancing Science, Improving Care
Chasing the Sun
24 hours of COVID-19 followed by IDWeek

https://bit.ly/2YbrasA