Introduction: Nosocomial infections caused by multidrug resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas* are increasing in frequency and are difficult to treat. The newer cephalosporin – beta lactamase inhibitor combinations, ceftolazane-tazobactam (C-T) and ceftazidime-avibactam (CZA) have demonstrated activity against *Pseudomonas aeruginosa* isolates with activity against isolates resistant to ceftazidime alone or piperacillin-tazobactam.

Cephalosporin components of both agents have in-vitro bactericidal activity by inhibition of cell wall biosynthesis by binding to penicillin-binding proteins. CZA also has shown in vitro activity against *P. aeruginosa* in the presence of some AmpC beta-lactamases, and some strains without outer membrane porin (OpRD). Both cephalosporin-beta lactamase inhibitor antibiotics C-T and CZA are currently approved for use with complicated intra-abdominal infections with addition of metronidazole or complicated urinary tract infections including Pyelonephritis. Use for other infectious indications is not currently approved by the FDA. Published articles showcasing ceftolazane-tazobactam (C-T) have reported successful treatment of lower respiratory tract infections in off-label use where MDR *Pseudomonas aeruginosa* was isolated.

**Methods:** Susceptibility testing was performed using E-test agar diffusion methods for 46 clinical isolates of MDR / XDR *Pseudomonas aeruginosa* and 1 reference strain of *P. aeruginosa* (ATCC 27853) with testing against all 47 isolates against ceftolazane-tazobactam (C-T) and 46 against ceftazidime-avibactam (CZA).

28 organisms were isolated from respiratory secretions with >90% recovered in burn intensive care setting from tracheal aspiration, 9 from wounds not from an intra-abdominal source, 7 from urine, and 2 from blood. 27 were classified as MDR while 19 were XDR. Isolates labeled as MDR met criteria as "acquired non-susceptibility to at least one agent in 3 or more antimicrobial categories, while XDR was more specific to include "non-susceptibility to at least one agent in all but 2 or fewer antimicrobial categories." 7

Clinical and reference isolates were inoculated onto Mueller-Hinton agar diluted to a 0.5 McFarland suspension with application of E-test to agar surface with quality control performed as per CLSI standards. Isolates were read at 24 hours incubation. Minimum inhibitory concentration (MIC) was read at the intersection of the clear ellipse zone of growth to the E-test strip representing 100% inhibition of visible growth.

Breakpoints for susceptibility include susceptible at <=<4/4, intermediate at 8/4 and resistant at >16/4 for ceftolazane-tazobactam (C-T), and susceptible at <=8/4, and resistant at >16/4 for ceftazidime-avibactam (CZA).

**Results:** The modal MIC for ceftolazane-tazobactam (C-T) was 0.75 mcg/mL and for ceftazidime-avibactam (CZA) was 2 mcg/mL. (Table 1)

The MICs at which 50% of the isolates tested were inhibited (MIC50) for C-T was 3 and for ceftazidime-avibactam (CZA) was 4. The MICs at which 90% of the isolates tested were inhibited (MIC90) for C-T was >128 and for ceftazidime-avibactam (CZA) was 32. (Table 2)

65% of isolates demonstrated susceptibility to ceftolazane-tazobactam (C-T) at <=<4/4, while 78% of isolates were susceptible to ceftazidime-avibactam (CZA) at <=8/4. (Table 2)

**Conclusion:**

- Results of antimicrobial agent testing demonstrate the potential of ceftolazane-tazobactam (C-T) and ceftazidime-avibactam (CZA) to treat susceptible isolates of MDR/XDR *Pseudomonas*.

- Results support consideration of these agents as an option particularly to treat ventilator associated respiratory tract infections with MDR/XDR *Pseudomonas* recovered as a pathogen where extensive resistance leaves no alternative for standard antimicrobial intervention and where use of colistin is not advised or the organism is resistant.

**References:**