Ceftolozane-Tazobactam and Meropenem Synergy Testing Against Multi-Drug and Extensively Drug-Resistant *Pseudomonas aeruginosa*

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BACKGROUND

- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa* (PA) have limited therapeutic options for treatment.
- Ceftolozane/tazobactam is a newer anti-pseudomonal drug effective against resistant PA infections, however resistance against this drug has now also developed.
- A study by Montero et al (2018) demonstrated that the combination of ceftolozane/tazobactam and meropenem against an XDR PA high-risk clone showed significant bacterial density reduction and suppression of resistance for the duration of the study.
- In this study, we explored the combination of ceftolozane/tazobactam (CT) and meropenem (MP) as a possible effective regimen against MDR and XDR PA.

METHODOLOGY

- We obtained 33 non-duplicate isolates of MDR and XDR PA grown from blood, urine and respiratory samples collected from patients admitted between 2015 and 2019 at our two affiliate teaching hospitals.
- MDR PA was defined as resistance to 3 or more classes of anti-pseudomonal antibiotics, and XDR PA as resistance to all but two or less classes of anti-pseudomonal antibiotics. Antimicrobial preparations of both MP and CT were made according to manufacturer instructions.

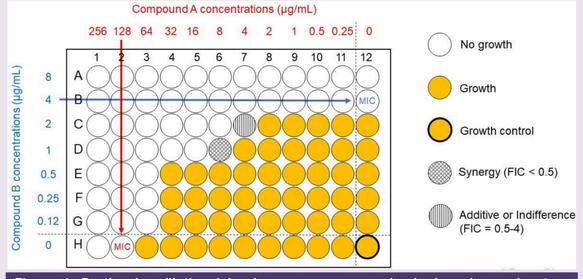

Figure 1. Broth microdilution (also known as synergy checkerboard assay) set up. Columns 1 to 11 containing 2-fold serial dilutions of Compound A; rows A to G containing 2-fold serial dilutions of Compound B. Syngergistic effect shown in well D6. [Credit: Emery Pharma, "Antimicrobial Synergy Study- Checkerboard Testing."]

- Susceptibility testing was performed using the broth microdilution method following CLSI guidelines. The ATCC 27853 strain of PA used as control.
- Results were interpreted by a trained researcher. Synergy, additive effect, indifference and antagonism were defined as FIC (fractional inhibitory concentration) indices of ≤0.5, >0.5 to <1, >1 to <4, and >4, respectively.

RESULTS

- Thirteen (39%) of 33 PA isolates were classified as XDR, while 20 (61%) PA isolates were MDR.
- All isolates were resistant to MP, while only 2 (6%) isolates were susceptible to CT.

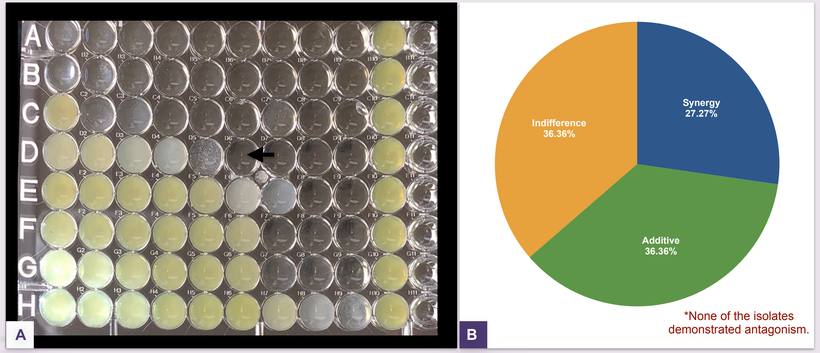

Figure 2. A) Broth microdilution 96-well plate set-up used in the study. Colums 1 to 9 containing 2 fold serial dilutions of ceftolozane/tazobactam; rows A to G containing serial 2-fold dilutions of meropenem. Synergistic effect seen in well D6 (depicted by arrow). Positive and negative controls in columns 10 and 11, respectively. B) Synergistic effect seen in 9 (27.3%) isolates, additive effect seen in 12 (36.4%) isolates, and indifference seen in 12 (36.4%) isolates . None of the isolates demonstrated any antagonistic effect.

- A synergistic effect was seen in 9 (27.3%) of PA isolates— 2 of which were XDR PA, and 7 were MDR PA.
- An additive effect was seen in 12 (36.4%), with indifference seen in 12 (36.4%) of isolates.
- For all 33 isolates, MIC50 was >32 ug/mL for meropenem alone, but decreased to 16 ug/mL when combined with CT. MIC50 was 64 ug/mL for ceftolozane alone, but decreased to 16 ug/mL when combined with MP.
- In this study, no antagonism was seen when CT and MP were combined.

CONCLUSION

- When used in combination, CT and MP can exert a synergistic effect against MDR and XDR PA. Additive effect and indifference can also be seen when both antibiotics were used.
- A substantial decrease in MIC50 was seen for both antibiotics were seen when used in combination. Moreover, there was no antagonism seen when both antibiotics were combined.
- This study shows that the use of CT and MP in combination may be a viable option against XDR and MDR PA infections.

REFERENCES

1. Cabot, G et al, 2014. "*Pseudomonas aeruginosa* Ceftolozane-Tazobactam Resistance Development Requires Multiple Mutations Leading to Overexpression and Structural Modification of AmpC." Journal of Antimicrobial Agents and Chemotherapy, Vol 58, No.6, pp 3091-3099.
2. Clinical and Laboratory Standards Institute (CLSI), 2012. "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Ninth Edition."
3. Emery Pharma. "Antimicrobial Synergy Study—Checkerboard Testing." <https://emerypharma.com/biology/antimicrobial-synergy-study-checkerboard-assay/>
4. Montero, M et al, 2018. "Evaluation of Ceftolozane-Tazobactam in Combination with Meropenem against *Pseudomonas aeruginosa* ST175 in a Hollow-Fiber Infection Model." Journal of Antimicrobial Agents and Chemotherapy, <DOI: 10.1128/AAC.00026-18>.