Pharmacodynamics of ceftazidime-avibactam monotherapy and combination regimens against carbapenemase-producing *Klebsiella pneumoniae* measured by bloodculture system time to positivity (Tpos)

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Background

- Time-to-positivity (Tpos) is a commonly reported index in bloodculture systems that can be adapted to measure bactericidal activity in the patient's bloodstream during antibiotic therapy.
- We examined how simulated serum concentrations of ceftazidime-avibactam (CZA), meropenem (MEM), gentamicin (GEN), tigecycline (TGC), colistin (CST) or aztreonam (ATM) alone, or in combination, impacted Tpos measured against test inocula of KPC and NDM-carbapenemase producing *K. pneumoniae* (KP).

Materials and Methods

- We tested two KPC-2 and one NDM-2 carbapenemase-producing KP isolates.
- We analyzed how inoculum affects Tpos (3x10^1-3x10^8 CFU/ml) prepared in standard BacT/ALERT aerobic bloodculture bottles without inactivating matrix.
- We then inoculated 1 mL of human serum spiked with antibiotic concentrations/combinations simulating a range of human antibiotic exposures into bloodculture bottles containing (1x10^4 CFU/mL) of test isolates. Tpos was then measured over a 24-hour incubation period using standard incubator settings.
- The relationship of Tpos vs. antibiotic concentration was fitted to 4-parameter logistic regression model to estimate EC_{50}/EC_{90}.
- For combinations, a predicted null-response (Bliss-independence) interaction model was compared to the observed Tpos in the antibiotic combination array to identify synergistic or antagonistic interactions.

Results

- In antibiotic-freeserum, all isolates demonstrated a linear relationship between Tpos of 9.4-10.8 h to 4.5-5.2 h over an inoculum range of3x10^1 to 3x10^8 CFU/mL.
- A consistent dose-response relationship between Tpos and serum antibiotic exposures was observed for all antibiotics with the Tpos EC_{50} of ~16 hr evident at 1xMIC (Fig 1).

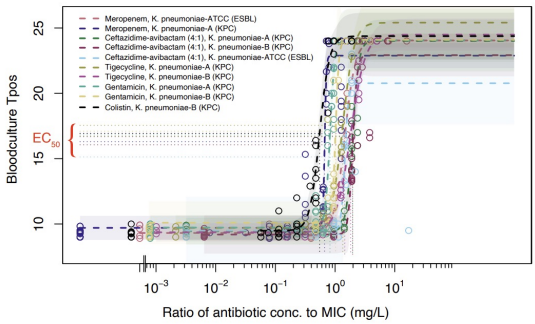

Figure 1. Antibiotic pharmacodynamic relationship to Tpos. A 4-parameter logistic regression model was fitted to serum antibiotic concentration data/isolate MIC. The EC50 is indicated by dotted lines. Shading represents 95% of the predicted Tpos response. R2 > 92% for fitted data.

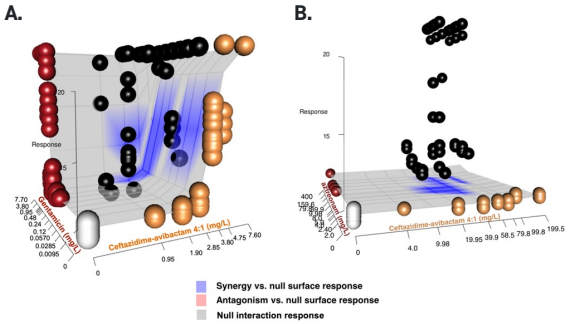

Figure 2. Example Bliss-independence interaction data for antibiotic combinations. (A) CZA + GEN against KPC-3 producing K. pneumoniae; (B) CZA + ATM against NDM-2 producing K. pneumoniae. The grey surface represents predicted null response of combination from fitted PD data of each single agent (observed data of red and yellow points). Black data points represent observed combination effects above or below predicted Bliss null response. Blue shading of the surface is indicative of antibiotic combinations producing synergistic interaction.

Table 1. Mean Tpos change observed with combinations against carbapenemase-producing *Klebsiella pneumoniae*

Antibiotic Combination	Test isolate (CAZ/AVI MIC µg/mL)	Mean Tpos change (hr) from Bliss independence predicted null response model (± 95% CI)
CZA + GEN	KP-A, KPC-3 carbapenemase (2)	+ 5.68 (5.09-6.53)
CZA + GEN	KP-B, KPC-3 carbapenemase (1)	+ 3.05 (2.16-4.03)
CZA + GEN	KP-Catania, KPC-3 carbapenemase (16)	+ 3.23 (2.10-4.14)
CZA + COL	KP-B, KPC-3 carbapenemase (1)	+ 2.31 (1.40-3.20)
CZA + TGC	KP-B, KPC-3 carbapenemase (1)	+ 1.66 (0.72-2.73)
CZA + ATM	KP-NDM, NDM-2 carbapenemase (>64)	+ 10.33 (10.32-10.34)
CZA + ATM	KP-Catania, KPC-3 carbapenemase (16)	+ 10.36 (10.31-10.35)
CZA + MER	KP-B, KPC-3 carbapenemase (1)	+ 11.61 (11.05-11.95)
CZA + MER	KP-Catania, KPC-3 carbapenemase (16)	+ 3.04 (2.15-4.03)

CZA- ceftazidime/avibactam; GEN- gentamicin; COL-colistin; TGC-tigecycline; ATM-aztreonam; MER-meropenem

- Combination experiments revealed prolongation of Tpos for most antibiotic combinations (Table 1, Fig 2a)
- The greatest improvement in Tpos was observed with CZA + ATM against the KPC-producing KP and NDM-producing KP, and CAZ + MER against KPC-producing KP (Table 1, Fig 2b.)

Conclusions

- Tpos was a robust and reproducible indicator of antimicrobial activity in serum that capable of detecting synergistic antibiotic interactions.
- Further test optimization could support the use of this simple monitoring approach of antimicrobial activity in patient serum.

For more information visit the ACUTE project website: www.acuteblood.com

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