MIC Profiling of Ceftazidime-Avibactam (CAZ/AVI) Against Two Carbapenemase-producing *Klebsiella pneumoniae* Isolates

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BACKGROUND

- Carbapenemases confer resistance against a broad range of β-lactams with a prevalence of 40-60% among carbapenem-resistant Enterobacteriaceae.
- CAZ-AVI is commonly used to treat infections due to carbapenemase-producing Enterobacteriaceae, typically guided by susceptibility testing with a single AVI concentration.
- This methodology does not take into consideration varying inhibitor concentration observed *in vivo* and may not reliably predict positive clinical outcomes.

OBJECTIVE

- To investigate a novel susceptibility testing method to guide CAZ-AVI therapy.

METHODS

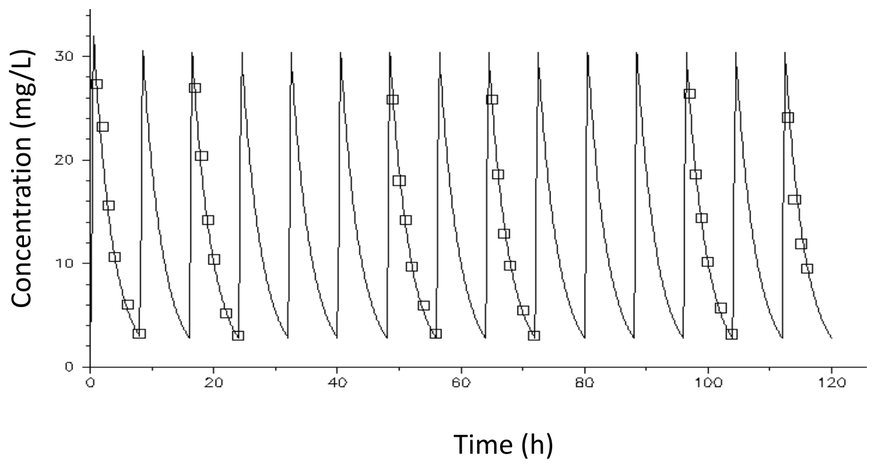
- Two bloodstream *K. pneumoniae* isolates (CAZ/AVI susceptible) from an abdominal source were recovered from 2 unrelated patients.
- Both patients were treated with CAZ/AVI, but had discordant outcomes: KP118 (eradication within 24h) and KP286 (persistent bacteremia for over 30 days).
- Carbapenemase production in the 2 isolates was confirmed via Carba NP test, and CAZ susceptibility was determined in a clinically relevant range of AVI concentration (0 - 16 mg/L).
- The concentration-response was characterized by the sigmoid inhibitory maximum effect (Emax) model.
- The best-fit parameter values were used to predict %T>MICi associated with CAZ/AVI exposures expected in peritoneal fluid after standard dosing (2.5g q8h).
- These CAZ/AVI exposures were simulated in the hollow-fiber infection model (HFIM), and the bacterial responses were correlated to observed clinical outcomes

RESULTS

Table 1: Best-fit parameters of the concentration-effect relationship

Bacteria	β-lactam	β-lactamase inhibitor	$\log_2(MIC_0)$	I_{max}	IC_{50}	H	r^2
KP118	Ceftazidime	Avibactam	9.00	12.06	0.96	0.79	0.99
KP286	Ceftazidime	Avibactam	6.98	10.51	2.40	1.07	0.99

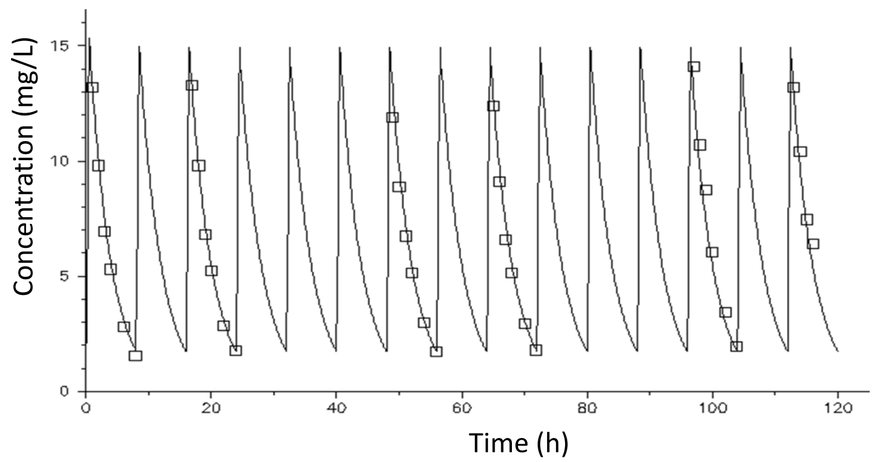
Figure 1: Simulated ceftazidime exposures in hollow-fiber infection model



Target Cmax = 30 mg/L
Target half-life = 2.5 h

R^2 = 0.984
Best-fit Cmax = 31 mg/L
Best-fit half-life = 2.2 h

Figure 2: Simulated avibactam exposures in hollow-fiber infection model

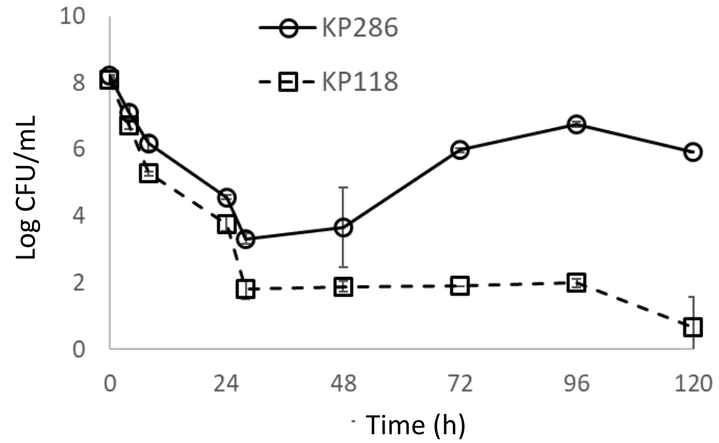


Target Cmax = 15 mg/L
Target half-life = 2.5 h

R^2 = 0.978
Best-fit Cmax = 15 mg/L
Best-fit half-life = 2.4 h

RESULTS

Figure 3: Bacterial responses to simulated CAZ/AVI exposures



CONCLUSIONS

- Considerable reduction in bacterial burden was observed within 24h for both isolates.
- Sustained suppression of KP118 was observed over 5 days, but not with KP286.
- MIC profiling better reflects bacterial response to changing β-lactamase inhibitor concentrations *in vivo* and is expected to be more robust than conventional susceptibility testing in predicting favorable patient outcome.

DISCLOSURES/FUNDING

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REFERENCES

- A complete reference list will be made available upon request.