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Pharmacodynamics of aztreonam/ceftazidime/avibactam and polymyxin B versus New Delhi MBL-producing Acinetobacter baumannii

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Background: *Acinetobacter baumannii* has become an increasingly urgent public health concern among global health agencies due to high rates of carbapenem resistance. Carbapenem-resistant *A. baumannii* (CRAB) that express both oxacillinases and MBLs is especially problematic due to resistance to all β-lactams.

Methods: Two clinical *A. baumannii* isolates, AR-0033 and AR-0083, harbouring bla_{NDM-1} (for both isolates $MIC_{aztreonam}$ >64 mg/L, $MIC_{ceftazidime/avibactam}$ >128/4 mg/L, $MIC_{polymyxin\ B}$ =1 mg/L, $MIC_{cefiderocol}$ ≥16 mg/L) were treated with mono- or combination therapies of aztreonam/ceftazidime/avibactam and polymyxin B (PMB) in static time–kill studies over 24 h. Replicate time–kills were analysed by integrating the area under the cfu/mL-versus-time curve using the linear-trapezoidal method and normalizing to the growth control to produce the log-ratio area (LRA). The LRA was mathematically modelled as a function of aztreonam concentrations using a Hill-type function to identify the IC_{50} values for aztreonam.

Results: Treatment with aztreonam/ceftazidime/avibactam achieved <2 $\log_{10}$ cfu/mL reduction by 24 h for all concentrations in both isolates. Monotherapies of PMB at 0.75, 1.5, 3.0 and 6.0 mg/L displayed maximum killing by 6 h against AR-0033. Monte Carlo simulations of human pharmacokinetics of aztreonam showed that package insert dosing resulted in a average free steady-state concentration above the target aztreonam IC_{50} values for AR-0033 ≥96% of time when in combination with ceftazidime/avibactam and PMB.

Conclusions: This study supports the potential utility of low-dose PMB therapy in combination with β-lactams to combat NDM-producing CRAB.

Introduction

Acinetobacter baumannii is a Gram-negative, aerobic, non-fermenting bacillus that frequently causes highly drug-resistant nosocomial infections.[1] *A. baumannii* is an increasingly urgent concern among global health agencies, with the CDC and WHO declaring carbapenem-resistant *A. baumannii* (CRAB), respectively, as an urgent and critical priority.[2,3] *A. baumannii* has a natural competency that allows it to readily acquire new antibiotic resistance genes and can survive for extended periods on healthcare facility surfaces, which has led to the need for new treatment options. Infections associated with *A. baumannii* often include bacteraemia, meningitis, pneumonia, and infections of the skin and soft tissues, surgical wounds, or urinary tract.[4,5] Reported mortality rates of CRAB infections range from 16% to 76%, depending upon site of infection and initial treatment.[2,6] Despite a reported decrease in total CRAB-associated infections—11 700 were reported by the CDC in 2012 compared with 8500 reported in 2017—there are still areas of the world with carbapenem resistance rates greater than 50%.[3]

MDR and XDR *A. baumannii* has become increasingly problematic due to the presence of class D carbapenemases (i.e. oxacillinase), MBLs or, most problematically, both. This surge in carbapenem resistance in *A. baumannii* has resulted in limited treatment options. NDM-1, an MBL, confers resistance to all β-lactams with the exclusion of aztreonam, whereas oxacillinases confer additional resistance to carbapenems and aztreonam.[7–9] The antibiotic pipeline for Gram-negative bacteria has largely focused on the development of novel β-lactamase inhibitors, but recently approved inhibitors have no activity against MBLs and only modest activity against oxacillinases.[10,11]

Because of the unique enzyme profile of CRAB, clinicians are often forced to use the polymyxins [polymyxin B and polymyxin E

(colistin)] as salvage therapy for CRAB infections, which have a narrow therapeutic window. Polymyxin doses are typically limited by neuro- and nephrotoxicity and therefore have a guideline-recommended maximum daily exposure [i.e. 24 h area under the concentration–time curve at steady state ($AUC_{ss,24}$)] of 100 mg h L^{-1}.[12] The current standard of care for NDM-harbouring Gram-negatives is treatment with either polymyxins or aztreonam-based combinations (typically with ceftazidime/avibactam). However, CRAB is intrinsically resistant to aztreonam, with neither CLSI nor EUCAST providing breakpoints. Thus, combating NDM-harbouring CRAB demands significant innovation to address this public health threat and develop rationally optimized combination therapies.

The main objective of this study was to evaluate the bacterial killing effects of polymyxin B alone and as a low-dose adjuvant to combination aztreonam/ceftazidime/avibactam therapy for the treatment of NDM-expressing, carbapenem-resistant *A. baumannii*. To achieve this goal, we studied humanized concentrations of each antibiotic *in vitro* against two clinical isolates of *A. baumannii* that both expressed NDM-1.

Methods

Bacterial isolates, antibiotics and media

Experiments were conducted using two NDM-1–harbouring *A. baumannii* isolates: AR-0033 and AR-0083 (both isolates: $MIC_{aztreonam}$ >64 mg/L, $MIC_{ceftazidime/avibactam}$ >128/4 mg/L, $MIC_{polymyxin\ B}$ = 1 mg/L, $MIC_{cefiderocol}$ ≥16 mg/L). MICs for both isolates were determined via broth microdilution in duplicate according to CLSI. AR-0033 harbours the β-lactamase genes bla_{NDM-1} and bla_{OXA-94}; comparatively, AR-0083 harbours bla_{NDM-1}, bla_{OXA-23}, bla_{OXA-69} and bla_{PER-7}. Avibactam (IMHA, Inc., Mount Prospect, IL, USA), aztreonam (AKSci, Union City, CA, USA), ceftazidime (Sigma Aldrich, St Louis, MO, USA) and polymyxin B (Sigma Aldrich, St Louis, MO, USA) were used for all studies and prepared fresh for each experiment and reconstituted using saline. CAMHB, supplemented with 25 mg/L calcium and 12.5 mg/L magnesium, and Mueller–Hinton agar (MHA) were used for all experiments.

Static time–kill studies

Static time–kill studies were conducted in CAMHB using mono- and combination therapies of aztreonam, ceftazidime/avibactam and polymyxin B. Monotherapies included a 2-fold aztreonam/ceftazidime/avibactam concentration array from 16.5/18.25/2.475 mg/L to 132/146/19.8 mg/L, and a 2-fold polymyxin B concentration array from 0.75 mg/L to 6.0 mg/L. Combination therapies included the 2-fold aztreonam/ceftazidime/avibactam concentration array plus the 2-fold polymyxin B concentration array. A target starting inoculum of 10^7 cfu/mL was used for all experiments, with each reaction vessel being incubated at 37°C in a water bath shaker. Samples were collected at 0, 1, 2, 4, 6, 8 and 24 h and plated on drug-free MHA after serial dilutions with saline. Colony counts were enumerated using a Protos 3 automated colony counter (Synbiosis, Cambridge, UK).

Data analysis

Data for each experiment were summarized by calculating the area under the cfu-versus-time curve (AUCFU) using the linear trapezoidal rule, as previously described.[13] The AUCFU for each time–kill was then normalized to the growth control and log_{10}-transformed to produce the log ratio area (LRA). Observed changes in LRA due to aztreonam concentrations were fit with a Hill-type function to identify maximum effect (I_{max}), the extent of drug effect ($I_{delta} = I_{max} I_0$), where I_0 is defined as the baseline drug effect normalized by the growth control, and drug sensitivity (IC_{50}).

Monte Carlo simulations

Clinically observed concentrations were compared with estimated IC_{50} values by generating pharmacokinetic (PK) profiles of aztreonam in simulated subjects using established PK models from the literature.[14,15] Aztreonam dosing was based on the package insert and implemented with two loading doses (i.e. 1 g × 1 at 0 h, and 2 g × 1 at 0 h) with three different maintenance regimens (i.e. 500 mg q8h at 8 h, 1 g q8h at 8 h, and 2 g q8h at 8 h) resulting in a maximum simulated dose of 6 g/day. For each tested dose regimen, 1000 simulated concentration–time profiles were generated to calculate the mean percent elapsed time over IC_{50}. Subject simulation data and plot generation were performed using the R software suite (v4.3.0; R Foundation, Vienna, Austria). Likewise, PK profiles of polymyxin B were generated using a similar established PK model, while implementing identical, guideline-recommended loading doses of 2 mg/kg of polymyxin B with five different maintenance regimens (i.e. 0.3125, 0.625, 1.25, 2.5 and 5 mg/kg q12h at 12 h) to determine relevant clinical polymyxin B average steady-state concentration ($fC_{ss,avg}$) and percentage of simulated subjects above the guideline-recommended $AUC_{ss,24}$.[12]

Results

Static time–kill studies

Results of static time–kill studies including aztreonam/ceftazidime/avibactam and polymyxin B monotherapy and combination therapies against both isolates of *A. baumannii* are summarized in Figure 1. Therapies of aztreonam/ceftazidime/avibactam with polymyxin B achieved greater than 2 log_{10} cfu/mL of bacterial reduction by 24 h for all concentrations and isolates. Monotherapies of polymyxin B at 0.75, 1.5, 3.0 and 6.0 mg/L displayed maximum bacterial killing between 4 and 6 h against AR-0033, with maximum reductions of 3.19, 3.17, 3.53 and 4.49 log_{10} cfu/mL, respectively. By comparison, the same polymyxin B concentrations resulted in maximum bacterial killing against AR-0083 between 4 and 8 h, with maximum reductions of 1.68, 2.66, 4.12 and 3.04 log_{10} cfu/mL, respectively. Despite initial bacterial killing, polymyxin B monotherapies resulted in regrowth by 24 h for both isolates.

All of the experimental polymyxin B concentrations when combined with aztreonam/ceftazidime/avibactam at 16.5/18.25/2.475 mg/L or 33/36.5/4.95 mg/L produced bactericidal activity (i.e. 99.9% reduction) against AR-0033, with maximum bacterial killing occurring between 6 and 8 h. Aztreonam/ceftazidime/avibactam concentrations of 16.5/18.25/2.475 mg/L coupled with polymyxin B at 0.75 and 1.5 mg/L achieved log_{10} cfu/mL reductions of 4.04 and 6.02 compared with starting conditions, before regrowing at 24 h. When coupled with polymyxin B at 3.0 and 6.0 mg/L, the treatments achieved transient bactericidal activity before regrowing at 24 h.

In a similar fashion, aztreonam/ceftazidime/avibactam concentrations of 33/36.5/4.95 mg/L coupled with polymyxin B at 0.75 and 1.5 mg/L achieved log_{10} cfu/mL reductions of 3.67 and 4.37, before regrowing at 24 h. When coupled with polymyxin B at 3.0 and 6.0 mg/L, the treatments also displayed bactericidal activity before regrowing at 24 h. All combinations of polymyxin B with aztreonam/ceftazidime/avibactam at 66/73/

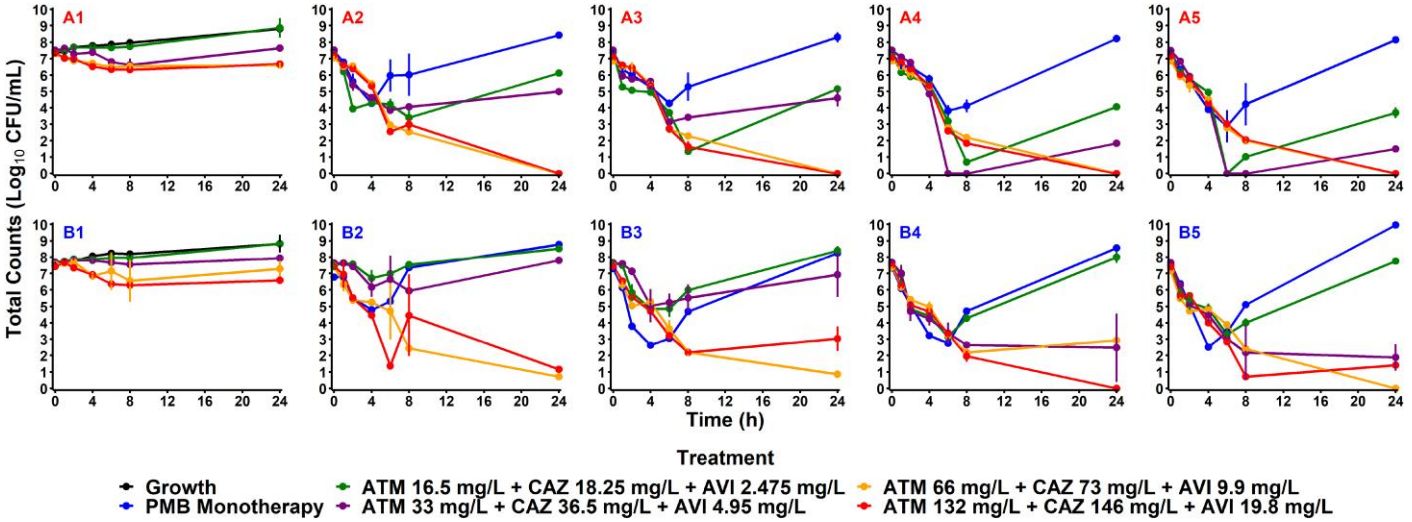

Figure 1. Static time–kill results of *A. baumannii* isolates versus combination β-lactam therapies with and without polymyxin B. Observed bacterial concentrations (cfu/mL) of *A. baumannii* isolates AR-0033 (A1–A5) and AR-0083 (B1–B5) over 24 h as mean (dots) and standard deviation (bars) from replicates. Plots are separated by polymyxin B adjuvant concentrations: polymyxin B 0.0 mg/L (A1/B1), polymyxin B 0.75 mg/L (A2/B2), polymyxin B 1.5 mg/L (A3/B3), polymyxin B 3.0 mg/L (A4/B4) and polymyxin B 6.0 mg/L (A5/B5). ATM, aztreonam; AVI, avibactam; CAZ, ceftazidime; PMB, polymyxin B.

9.9 mg/L or 132/146/19.8 mg/L achieved bactericidal activity against AR-0033 with no regrowth noted at 24 h.

Against AR-0083, combinations of polymyxin B at any experimental concentration with aztreonam/ceftazidime/avibactam at 16.5/18.25/2.475 mg/L or 33/36.5/4.95 mg/L, achieved maximum bacterial killing between 4 and 8 h. Polymyxin B at 0.75, 1.5, 3.0 and 6.0 mg/L with aztreonam/ceftazidime/avibactam at 16.5/18.25/2.475 mg/L achieved $\log_{10}$ cfu/mL reductions of 0.758, 2.81, 4.44 and 4.32, respectively, before regrowing at 24 h. Combinations of aztreonam/ceftazidime/avibactam 33/36.5/4.95 mg/L with polymyxin B at 0.75 and 1.5 mg/L achieved $\log_{10}$ cfu/mL reductions of 1.69 and 2.59 before regrowing at 24 h.

Select combinations of polymyxin B and aztreonam/ceftazidime/avibactam at 66/73/9.9 mg/L or 132/146/19.8 mg/L failed to maintain bactericidal activity at 24 h against AR-0083. Combinations of aztreonam/ceftazidime/avibactam at 66/73/9.9 mg/L with polymyxin B at 3.0 mg/L achieved bactericidal activity at approximately 8 h but showed regrowth by 24 h, whereas aztreonam/ceftazidime/avibactam at 132/146/19.8 with polymyxin B at 1.5 and 6.0 mg/L showed bactericidal activity at approximately 8 h but regrew by 24 h.

Hill-type function

Data from static time–kill studies were best fit with a Hill-type function and are summarized in Figure 2. Aztreonam/ceftazidime/avibactam concentrations yielded aztreonam IC_{50} values of 32.2 mg/L and 37.9 mg/L against AR-0033 and AR-0083. Upon adding polymyxin B at 0.75, 1.5, 3.0 and 6.0 mg/L to aztreonam/ceftazidime/avibactam combinations against AR-0033, subsequent IC_{50} values were reduced to 2.26, 0.0543, 0.141 and 3.90 mg/L, respectively. Addition of the same polymyxin B array to aztreonam/ceftazidime/avibactam combinations against AR-0083 reduced subsequent IC_{50} values to 34.1, 32.8, 21.7 and 25.3 mg/L, respectively.

Monte Carlo simulations

Simulated maintenance dosing regimens of aztreonam resulted in a $fC_{ss,avg}$ ± standard deviation (SD) of 5.27 ± 1.30 mg/L for the 500 mg q8h regimen, whereas 1 g q8h and 2 g q8h regimens resulted in $fC_{ss,avg}$ of 10.5 ± 2.61 mg/L and 21.1 ± 5.22 mg/L, respectively. No difference in $fC_{ss,avg}$ was observed between regimens using a 1 g loading dose, as opposed to a 2 g loading dose. Data from simulated dosing regimens were plotted as a function of percentage of time above the IC_{50} values of aztreonam in Figure 3.

Package insert dosing of aztreonam, using a 2 g loading dose followed by 2 g q8h starting at 8 h resulted in simulated subjects having a mean $fC_{ss,avg}$ above the estimated IC_{50} for aztreonam in the presence of ceftazidime/avibactam for 58.9% of time for AR-0083. Addition of the polymyxin B array at 0.75, 1.5, 3.0 and 6.0 mg/L to aztreonam/ceftazidime/avibactam increased the percentage of time above the estimated IC_{50} to 64.5%, 65.4%, 80.9% and 75.7%, respectively. In contrast, simulated subjects with an identical regimen had a median $fC_{ss,avg}$ above the estimated IC_{50} for aztreonam in the presence of ceftazidime/avibactam for 66.2% of time for AR-0033. Adding the same polymyxin B array increased the percentage of time to greater than 99% for all concentrations of polymyxin B.

Dosing of aztreonam at a 2 g loading dose, followed by 1 g q8h starting at 8 h resulted in simulated subjects having a mean $fC_{ss,avg}$ above the estimated IC_{50} for aztreonam in the presence of ceftazidime/avibactam for 25.9% of time for AR-0083. The percentage of time above the estimated IC_{50} was increased to 31.6%, 33.7%, 54.6% and 47.2% upon addition of the

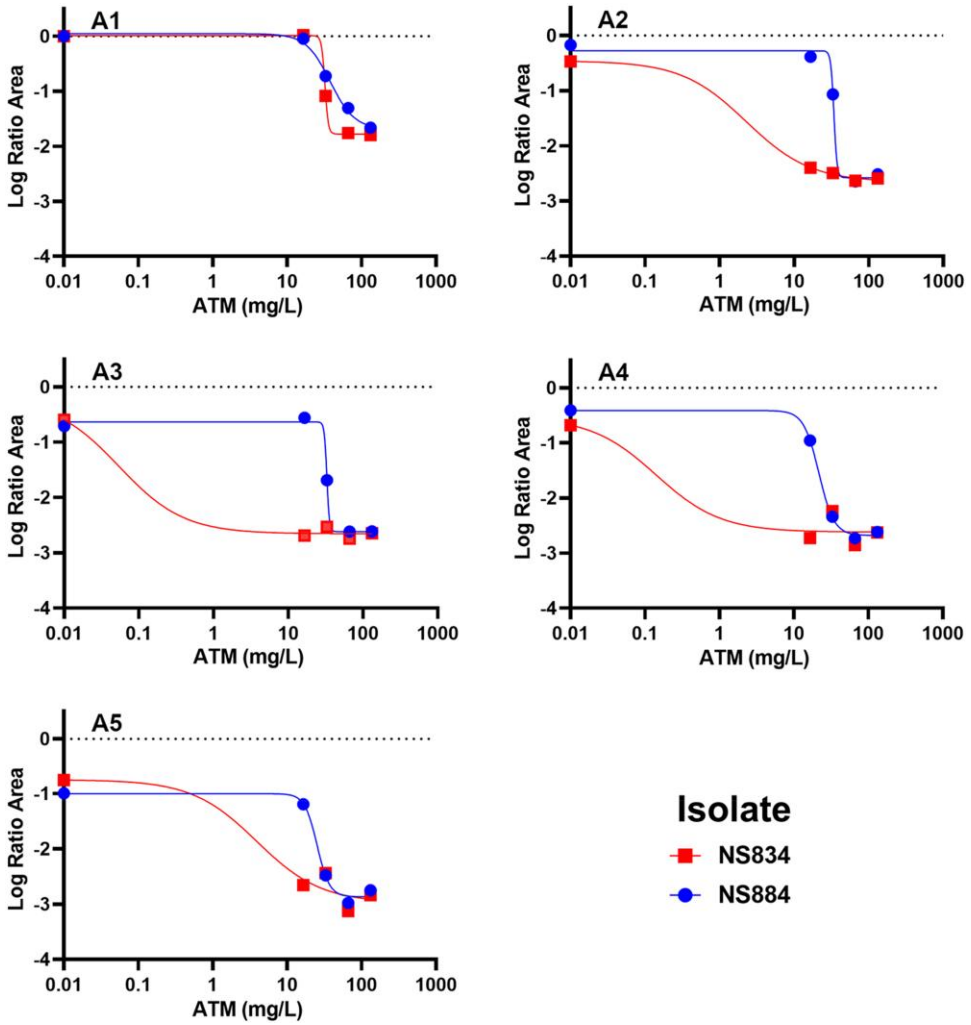

Figure 2. Hill-type function modelled over observed log ratio area. A Hill-type function modelled over recorded changes in growth-normalized log ratio area due to polymyxin B concentrations to determine I_{max} and IC_{50}. Aztreonam (ATM) concentrations are in the aztreonam/ceftazidime/avibactam combination therapy ratio of 1.1:0.15:1. Plots are separated by polymyxin B adjuvant concentrations: polymyxin B 0.0 mg/L (A1), polymyxin B 0.75 mg/L (A2), polymyxin B 1.5 mg/L (A3), polymyxin B 3.0 mg/L (A4) and polymyxin B 6.0 mg/L (A5).

polymyxin B array. Comparatively, simulated subjects with an identical regimen had a mean $fC_{ss,avg}$ above the estimated IC_{50} for aztreonam in the presence of ceftazidime/avibactam for 34.7% of time for AR-0033. The addition of the same polymyxin B array increased the percentage of time to greater than 99% for all concentrations of polymyxin B except polymyxin B 6.0 mg/L, which increased to 97.6%.

Aztreonam dosing regimens at a 2 g loading dose, followed by 500 mg q8h starting at 8 h resulted in simulated subjects having a mean $fC_{ss,avg}$ above the estimated IC_{50} for aztreonam in the presence of ceftazidime/avibactam for 3.3% of the time for AR-0083. When adding the polymyxin B array, subsequent percentages above the estimated IC_{50} were increased to 4.6%, 5.1%, 21.1% and 13.5%, respectively. In comparison, simulated subjects with an identical regimen had a mean $fC_{ss,avg}$ above the estimated IC_{50} for aztreonam in the presence of ceftazidime/avibactam for 5.4% of the time for AR-0033. Upon addition of the polymyxin B array, subsequent percentages above the estimated IC_{50} were increased to 96.8%, 99.9%, 99.9% and 90.2%, respectively.

Regarding polymyxin B, simulations of critically ill subjects using a polymyxin B maintenance regimen of 0.3125 mg/kg produced a median $fC_{ss,avg}$ of 0.400 ± 0.141 mg/L. Increasing the polymyxin B maintenance regimens 2-fold to 5 mg/kg produced median $fC_{ss,avg}$ values of 0.788 ± 0.271 mg/L, 1.57 ± 0.533 mg/L, 3.13 ± 1.06 mg/L, and 6.26 ± 2.10 mg/L, respectively. The 2.5 mg/kg and 5 mg/kg maintenance regimens had 16.8% and 90.2% of simulated subjects above the guideline-recommended $AUC_{ss,24}$ of 100 mg h L^{-1}, whereas the 0.3125, 0.625 and 1.25 mg/kg maintenance regimens had 0% of simulated subjects above the guideline-recommended $AUC_{ss,24}$.[12]

Discussion

The rise and propagation of MDR and XDR *A. baumannii* in clinical settings has prompted the need for new combination therapies.

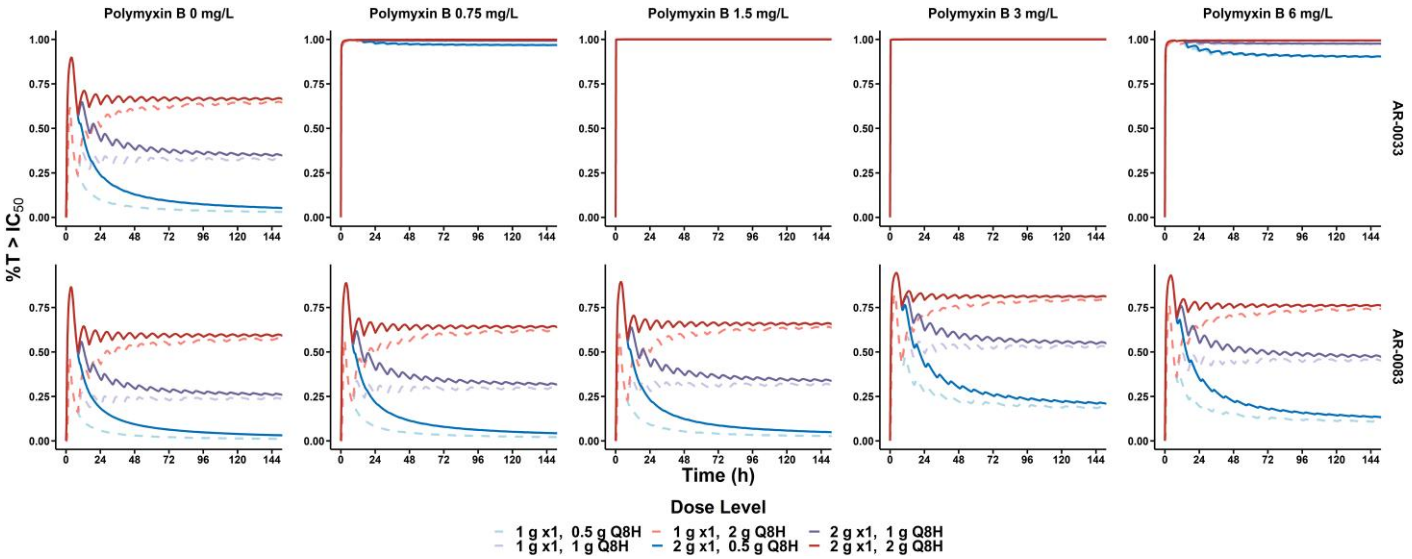

Figure 3. Percentage of time above estimated IC_{50} values of aztreonam. Six simulated dosing regimens over the course of 144 h to determine the percentage of time a simulated subject would have a $fC_{ss,avg}$ above the estimated aztreonam IC_{50} value. Aztreonam was simulated as a maintenance dose of 500 mg, 1 g or 2 g every 8 h, with either a 1 g (light-shaded dashed line) or 2 g (dark-shaded solid line) loading dose.

Combinations of ceftazidime/avibactam plus aztreonam have been successful against NDM-1–harbouring Enterobacterales.[16,17] Yet, when this combination triple therapy was used against *A. baumannii* isolates AR-0033 and AR-0083 in this study, all combinations of aztreonam/ceftazidime/avibactam failed to produce at least a 2 $\log_{10}$ cfu/mL bacterial killing, further indicating the need for alternative strategies against MBL-harbouring *A. baumannii*.

Treatment with polymyxins is a last-line option against CRAB, but this strategy is limited by dose-dependent toxicities and resistance development.[18] To combat this, polymyxin B was tested as a low-, normal- and high-concentration adjuvant administered alongside aztreonam/ceftazidime/avibactam. Aztreonam/ceftazidime/avibactam and polymyxin B combination therapy resulted in bactericidal activity against AR-0033. When this procedure was repeated against AR-0083, therapeutic and supratherapeutic concentrations of aztreonam/ceftazidime/avibactam combinations yielded minor additional bacterial killing when compared with polymyxin B monotherapy.

The mechanisms of polymyxin B synergy on β-lactams appear multifactorial, related to the direct killing effects of each drug, cross-coverage of resistant subpopulations, and mechanistic synergy. Regarding mechanistic synergy, it is hypothesized that polymyxin B acts with detergent-like properties at the outer membrane, leading to increased β-lactam target site concentrations through enhanced β-lactam permeability.[19] Potential limitations of aztreonam/ceftazidime/avibactam therapy in this study may be due to the common β-lactamases expressed in *A. baumannii* compared with the Enterobacterales. Specifically, *A. baumannii* AR-0083 harbours bla_{PER-7} and bla_{OXA-23}, which have been shown to produce rapid hydrolysis of aztreonam, unlike bla_{OXA-94} of AR-0033, which degrades aztreonam more slowly.[20] This is supported by the initial reduction of approximately 93% in aztreonam drug IC_{50} when polymyxin B 0.75 mg/L was added to aztreonam/ceftazidime/avibactam against AR-0033, whereas AR-0083 only had an approximate 9% reduction in aztreonam IC_{50}.

Simulated clinical trials of aztreonam therapy provide additional insights into estimating the probability of target attainment by allowing the prediction of the *in vivo* response with only *in vitro* observations.[14,15] Simulated package insert regimens of aztreonam for subjects with severe systemic or life-threatening infections showed that simulated subjects receiving both aztreonam and polymyxin B consistently exceeded the baseline percent time over IC_{50} target of aztreonam monotherapy for both strains. Simulated AR-0033 subjects exceeded the observed aztreonam IC_{50} efficacy targets over 99% of time at the maximum simulated dose of 2 g q8h. Meanwhile, simulated AR-0083 subjects in an identical regimen exceeded the observed aztreonam efficacy targets for at least 64% of time.

Simulated guideline dosing of polymyxin B resulted in no simulated subjects exceeding guideline maximum exposure of 100 mg h L^{-1}. Only among supratherapeutic maintenance regimens did simulated subjects exceed the guideline maximum toxicity threshold, with the 2.5 mg/kg and 5 mg/kg regimens resulting in 16.8% and 90.2% of simulated subjects being above the guideline maximum toxicity threshold. These data support the use of previously reported de-escalation strategies for polymyxin B in cases of combination use, which can result in human exposures below guideline-based limits of dosing.[12,21]

This study is principally limited by the number of isolates studied, variety of MBLs studied and use of static concentrations. As the studies were conducted at static concentrations, no information regarding drug effects under dynamic concentrations was generated. Future studies could address this through exploration of treatment regimens in a dynamic chemostat model, hollow-fibre infection model or other *in vivo* experimentation methods. In summary, low-dose concentrations of polymyxin B were synergistic with aztreonam/ceftazidime/avibactam concentrations that reflected clinical

fC_{max} and produced bactericidal activity against both AR-0033 and AR-0083. Ultimately, further research is needed to develop therapies against the growing threat of *A. baumannii* co-expressing MBL and OXA.

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Transparency declarations

We have no conflicts of interest to declare.

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