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Early initiation of three-drug combinations for the treatment of carbapenem-resistant *A. baumannii* among COVID-19 patients

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Objectives: We evaluated the clinical characteristics and outcomes of patients with COVID-19 who received three-drug combination regimens for treatment of carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections during a single-centre outbreak. Our objective was to describe the clinical outcomes and molecular characteristics and *in vitro* synergy of antibiotics against CRAB isolates.

Materials and methods: Patients with severe COVID-19 admitted between April and July 2020 with CRAB infections were retrospectively evaluated. Clinical success was defined as resolution of signs/symptoms of infection without need for additional antibiotics. Representative isolates underwent whole-genome sequencing (WGS) and *in vitro* synergy of two- or three-drug combinations was assessed by checkerboard and time-kill assays, respectively.

Results: Eighteen patients with CRAB pneumonia or bacteraemia were included. Treatment regimens included high-dose ampicillin-sulbactam, meropenem, plus polymyxin B (SUL/MEM/PMB; 72%), SUL/PMB plus minocycline (MIN; 17%) or other combinations (12%). Clinical resolution was achieved in 50% of patients and 30-day mortality was 22% (4/18). Seven patients had recurrent infections, during which further antimicrobial resistance to SUL or PMB was not evident. PMB/SUL was the most active two-drug combination by checkerboard. Paired isolates collected before and after treatment with SUL/MEM/PMB did not demonstrate new gene mutations or differences in the activity of two- or three-drug combinations.

Conclusions: Use of three-drug regimens for severe CRAB infections among COVID-19 resulted in high rates of clinical response and low mortality relative to previous studies. The emergence of further antibiotic resistance was not detected phenotypically or through WGS analysis. Additional studies are needed to elucidate preferred antibiotic combinations linked to the molecular characteristics of infecting strains.

Introduction

Acinetobacter baumannii is a difficult to treat nosocomial pathogen with a propensity for acquiring resistance against commonly used antibiotics. A significant proportion of isolates are carbapenem-resistant *A. baumannii* (CRAB) that are often missed empirically, and receipt of inactive therapy is a strong predictor of patient mortality.[1,2] Current treatment options include polymyxins, tetracycline derivatives, such as tigecycline and eravacycline, and aminoglycosides, although none of these are ideal options due to their pharmacokinetic limitations and toxicity.[3] Newer antimicrobial agents such as cefiderocol offer an alternative option; however, early clinical data did not demonstrate improved outcomes for patients with CRAB infections compared to best available therapy.[4] As concerning, two randomized clinical trials have not shown any benefit for the combination of colistin plus meropenem when compared to colistin alone for treatment of CRAB infections.[5,6] Thus, designing treatment regimens that are both safe and effective for CRAB infections remains a major challenge. *In vitro* data indicate that combination therapies including high-dose ampicillin/sulbactam with a carbapenem and a polymyxin demonstrate potent activity, but clinical data are limited to small case series including patients infected with colistin-resistant *A. baumannii*.[5,6] Expert guidance from the Infectious Diseases Society of America now recommends ampicillin-sulbactam as a preferred single agent for mild infections. For

moderate to severe CRAB infections, combination therapy with at least two *in vitro* active agents is suggested; however, which agents should be preferred over others is still unknown.[7]

We encountered a single-centre outbreak of CRAB infections among patients with severe COVID-19. Our locally developed institutional guidance prioritized an initial three-drug combination regimen given the limitations of the aforementioned treatment options. In this study, we aimed to evaluate the efficacy of this standardized approach to gain new insights into the treatment of CRAB infections. The specific objectives were to (i) define the clinical characteristics and outcomes of patients with infections due to CRAB treated with three-drug combination antibiotic therapy, (ii) determine the molecular epidemiology of infecting strains and (iii) explore *in vitro* synergy of two- and three-drug combination regimens using isolates from treated patients.

Materials and methods

Patients and bacterial isolates

Adult patients with severe COVID-19 admitted to the University of Maryland Medical Center between April and July 2020 with positive blood or respiratory cultures growing CRAB were identified. Only patients treated with initial three-drug antibiotic combinations were included. Optimized antibiotic regimens were used, which included high-dose ampicillin/sulbactam 9 g every 8 hours as a prolonged infusion over 4 hours, meropenem 2 g every 8 hours over 3 hours, minocycline 200 mg every 12 hours over a 1 hour and a polymyxin B 25 000 IU/kg loading dose followed by 15 000 IU/kg every 12 hours given over a 2-hour infusion. All agents were renally dose adjusted when applicable.[6,8,9] Treatment regimens were selected by the patient care team and continued throughout the treatment course unless modifications were made due to adverse effects (e.g. discontinuation of polymyxin B secondary to renal toxicity). Isolates collected before (initial) and after (recurrent) treatment were stored at −80°C until analysis.

Ethics

The study was approved by the institutional review board at the University of Maryland, Baltimore (HP-00092949).

Clinical data

Patient demographics, underlying medical conditions, sequential organ failure assessment (SOFA) score at the time of CRAB infection (culture collection), antibiotic therapy received before and after isolation of CRAB, and characteristics of the infection were collected. Pneumonia was defined by the isolation of CRAB in a pulmonary specimen, radiographic evidence of pneumonia, and signs and symptoms of infection. Diagnoses were confirmed by Infectious Diseases (ID) consultants caring for the patient. Clinical success was adjudicated by three independent investigators and defined as complete resolution of signs and symptoms of infection without a change or need for additional antibiotics at the end of the intended treatment course. Indeterminate outcomes were defined as either persistence of symptoms without evidence of infection or death due to severe COVID-19 infection that precluded classification as resolution or failure. Microbiologic failure was defined as subsequent isolation of CRAB from the respiratory tract or bloodstream after completion of the initial antibiotic course, or after >14 days of treatment if the initial treatment course was prolonged during the index admission. Recurrent pneumonia was defined as positive respiratory cultures with CRAB necessitating a repeat course of antibiotics within the same admission. All patients in the study were followed by ID consult services, and the diagnosis of both initial and recurrent pneumonia was confirmed by the ID consult team in the electronic medical record. Thirty-day all-cause mortality was assessed from the date of the index CRAB culture.

Organism identification and susceptibility testing

A. baumannii isolates were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on the Vitek MS (bioMérieux, Durham, NC, USA). For clinical care, antibiotic susceptibility was determined using Kirby–Bauer disc diffusion for meropenem, ampicillin/sulbactam, tigecycline, minocycline and amikacin in the microbiology laboratory at the University of Maryland Medical Center. MICs for amikacin were determined by gradient diffusion Etest strips (bioMerieux, Durham, NC, USA). Minimum inhibitory concentrations (MICs) of sulbactam, cefiderocol, colistin, eravacycline, meropenem, minocycline and tigecycline were determined by broth microdilution methods in *post hoc* analysis, and were not available to clinicians at the time of treatment. Cefiderocol MICs were determined in iron-depleted, cation-adjusted Mueller–Hinton broth. All MICs were determined in duplicate. If results did not agree, a third test was performed and the modal MIC reported. All MICs were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints.[10] *Pseudomonas aeruginosa* ATCC 27853 was used for quality control.

Whole-genome sequencing

Whole-genome sequencing (WGS) was performed as described previously.[11] Raw sequences were assembled using SPAdes v.3.14.1.[12] Core genome single-nucleotide polymorphism (cgSNP) differences between genome pairs were identified using Snippy v.4.4.5 (https://github.com/tseemann/snippy). Paired initial and recurrent isolates obtained from the same patient were compared using breseq.[13] β-lactamase genes were identified through CARD.[14] Raw sequence reads and draft genome assemblies have been deposited in the NCBI database under BioProject number PRJNA852776.

Synergy testing

In vitro synergy of two- or three-drug combinations was assessed by checkerboard and time-kill assays, respectively. Eight initial CRAB isolates from unique, representative patients were selected for checkerboard analysis of two-drug synergy between all possible combinations of meropenem, minocycline, polymyxin B and sulbactam. Synergistic and additive activity was defined as a fractional inhibitory concentration (FIC) ≤ 0.5 and 0.51–1 mg/L, respectively.[15]

Time-kill assays were performed as previously described using clinically achievable steady-state concentrations of meropenem (8 mg/L), polymyxin B (2 mg/L) and sulbactam (4 mg/L).[16] Tests were conducted using a starting concentration of 1×10^6 cfu/mL for each isolate. The log kills were calculated at 24 hours as the difference in log cfu/mL from the starting inoculum. Synergy was defined as a ≥2 log greater kill in combination compared to the most active single agent.

Results

Eighteen patients with CRAB ventilator-associated pneumonia (VAP; 13/18, 72%), bacteraemia (3/18, 17%), or hospital-acquired pneumonia (2/18, 11%) were included. At infection onset, the median SOFA score was 11 (range 4–17), 39% (7/18) were receiving extracorporeal membrane oxygenation (ECMO) and 89% (16/18) were in an intensive care unit (ICU) (Table 1). The median time from initial positive SARS-CoV-2 test to index CRAB culture was 16 days (range 4–41 days). Fifty-six percent (10/18), 72% (13/18) and 83% (15/18) of patients received three-drug combination therapy within 24-, 48- and 72-hours of initial CRAB cultures,

Table 1. Clinical characteristics, treatment regimens and outcomes of COVID-19 patients with invasive CRAB infections

Patient	Age	Sex	Type of infection	ICU	Charlson co-morbidity index	SOFA score	ECMO	Initial three-drug treatment regimen (treatment duration in days)	Clinical outcome	Microbiologic failure[a]	Recurrent pneumonia	Antibiotic-associated AKI[b]	30-day mortality	Inpatient mortality
BCU-1	20	M	BSI	Yes	0	17	Yes	SUL + MEM + PMB (14)	Resolution	Yes	—	No	No	No
MICU-1	26	M	VAP	Yes	0	15	No	SUL + MEM + PMB (21)	Failure	Yes	Yes	No	No	No
BCU-4	58	M	VAP	Yes	2	12	Yes	SUL + MEM + PMB (5)	Indeterminate	Yes	Yes	Yes	Yes	Yes
MICU-2	68	F	VAP	Yes	5	11	No	SUL + MEM + PMB (3)	Indeterminate	N/A	No	No	Yes	Yes
MICU-7	35	M	VAP	Yes	0	9	No	SUL + MEM + PMB (10)	Resolution	No	No	Yes	No	No
BCU-5	36	M	VAP	Yes	0	8	Yes	SUL + MEM + PMB (8)	Failure	Yes	Yes	No	No	No
MICU-9	33	F	VAP	Yes	1	10	No	SUL + MEM + PMB (8)	Resolution	N/A	No	No	No	No
BCU-6	50	M	VAP	Yes	1	12	Yes	SUL + MEM + PMB (8)	Indeterminate	Yes	No	No	No	No
MICU-11	57	M	VAP	Yes	2	7	Yes	SUL + MEM + PMB (14)	Resolution	Yes	Yes	No	No	No
MICU-13	79	F	BSI	Yes	6	8	No	SUL + MEM + PMB (14)	Resolution	No	—	No	No	No
BCU-8	51	F	VAP	Yes	3	4	Yes	SUL + MEM + PMB (10)	Resolution	Yes	Yes	Yes	No	No
BCU-9	52	M	VAP	Yes	1	7	Yes	SUL + MEM + PMB (10)	Failure	Yes	Yes	Yes	No	Yes
Other2	64	M	HAP	No	5	5	No	SUL + MEM + PMB (2)	Indeterminate	N/A	No	No	Yes	Yes
MICU-3	68	M	VAP	Yes	3	11	No	SUL + MIN + PMB (3)	Failure	N/A	No	Yes	Yes	Yes
MICU-8	77	F	VAP	Yes	4	11	No	SUL + MIN + PMB (8)	Resolution	No	No	Yes	No	No
MICU-12	61	M	VAP	Yes	7	12	No	SUL + MIN + PMB (10)	Resolution	Yes	Yes	No	No	Yes
Other1	47	F	HAP	No	3	4	No	MEM + MIN + PMB (14)	Resolution	N/A	No	Yes	No	No
MICU-10	43	F	BSI	Yes	1	16	No	SUL + MEM + MIN (35)	Failure	Yes	–[c]	No	No	Yes

BSI, bloodstream infection; ECMO, extracorporeal membrane oxygenation; F, female; HAP, hospital-acquired pneumonia; ICU, intensive care unit; M, male; MEM, meropenem; MIN, minocycline; PMB, polymyxin b; SUL, ampicillin-sulbactam; VAP, ventilator-associated pneumonia.

[a]Yes: repeat cultures with CRAB from the respiratory or bloodstream after completion of the initial antibiotic course; No: repeat cultures without CRAB; N/A: repeat cultures not obtained.

[b]Antibiotic associated acute kidney injury defined as a minimum of two increases in serum creatinine of at least 0.5 mg/dL or 50% or greater increase from baseline after several days of antibiotic therapy.

[c]Patient developed CRAB VAP on day 8 of BSI treatment course.

Table 2. *In vitro* susceptibility of representative baseline CRAB isolates from eight patients

	MIC (mg/L)							Fractional inhibitory concentration (interpretation)					
Patient-isolate	FDC	ERV	TGC	MIN	MEM	PMB	SUL	MEM + MIN	MEM + PMB	MEM + SUL	MIN + PMB	MIN + SUL	PMB + SUL
BCU1-1	0.25	0.5	1	4	>64	≤0.25	16	1.5 (I)	2 (I)	1 (I)	2 (I)	1 (I)	1 (I)
MICU13-1	0.12	0.5	1	4	>64	≤0.25	16	0.375 (S)	2 (I)	1.5 (I)	2 (I)	1 (I)	1 (I)
BCU4-0	0.12	0.5	1	4	>64	0.5	16	1.5 (I)	1.5 (I)	0.625 (A)	0.501 (A)	1 (I)	0.625 (A)
MICU10-1	0.25	0.5	1	4	>64	0.5	16	1.5 (I)	1.5 (I)	1.5 (I)	2 (I)	2 (I)	1 (I)
BCU9-1	0.12	0.5	1	4	>64	0.5	16	1.5 (I)	2 (I)	0.625 (A)	0.565 (A)	2 (I)	1 (I)
MICU-12-1	0.25	0.5	1	8	>64	≤0.25	8	1 (I)	2 (I)	1.25 (I)	2 (I)	1 (I)	0.75 (A)
MICU7-1	0.12	0.5	2	4	>64	≤0.25	8	1.5 (I)	2 (I)	2 (I)	2 (I)	1 (I)	0.625 (A)
MICU11-0	0.12	0.5	2	4	>64	0.5	8	1.5 (I)	2 (I)	1.5 (I)	1.5 (I)	1.5 (I)	0.56 (A)

FDC, Cefiderocol; ERV, Eravacycline; TGC, Tigecycline; MIN, Minocycline; MEM, Meropenem; PMB, Polymyxin B; SUL, Sulbactam.
Note. The following criteria was used to interpret fractional inhibitory concentration values: <0.5 = Synergy (S), 0.5–1 = Additive (A), >1 = Indifferent (I).

respectively. Treatment regimens included high-dose ampicillin/sulbactam, meropenem, plus polymyxin B (72%), ampicillin/sulbactam, minocycline, plus polymyxin B (17%) or other combinations (meropenem, minocycline, polymyxin b and ampicillin/sulbactam, meropenem, minocycline; 6% each). The median treatment duration was 10 days (range 2–35). Clinical success was achieved in 50% (9/18) of patients and did not differ across treatment regimens (Table 1). Microbiologic failures occurred in 56% (10/18) of patients, including 50% (4/8) of those with initial clinical success. Fifty-four percent (7/13) of patients with VAP experienced recurrent pneumonia. The overall 30-day mortality rate was 22% (4/18). COVID-19 was listed as the cause of death in 100% (4/4) of cases. Antibiotic-associated acute kidney injury occurred in 39% (7/18) patients.

Antibiotic MICs did not vary across initial isolates [Table 2, Table S1 (available as Supplementary data at *JAC* Online)]. The modal MICs for meropenem, minocycline, polymyxin b and ampicillin/sulbactam were >64, 8, 0.25 and 8 mg/L, respectively. Modal cefiderocol, eravacycline and tigecycline MICs were 0.12, 0.5 and 1 mg/L, respectively. Repeat susceptibility testing of recurrent isolates from patients who experienced microbiologic failures did not reveal further resistance following treatment (Table S1).

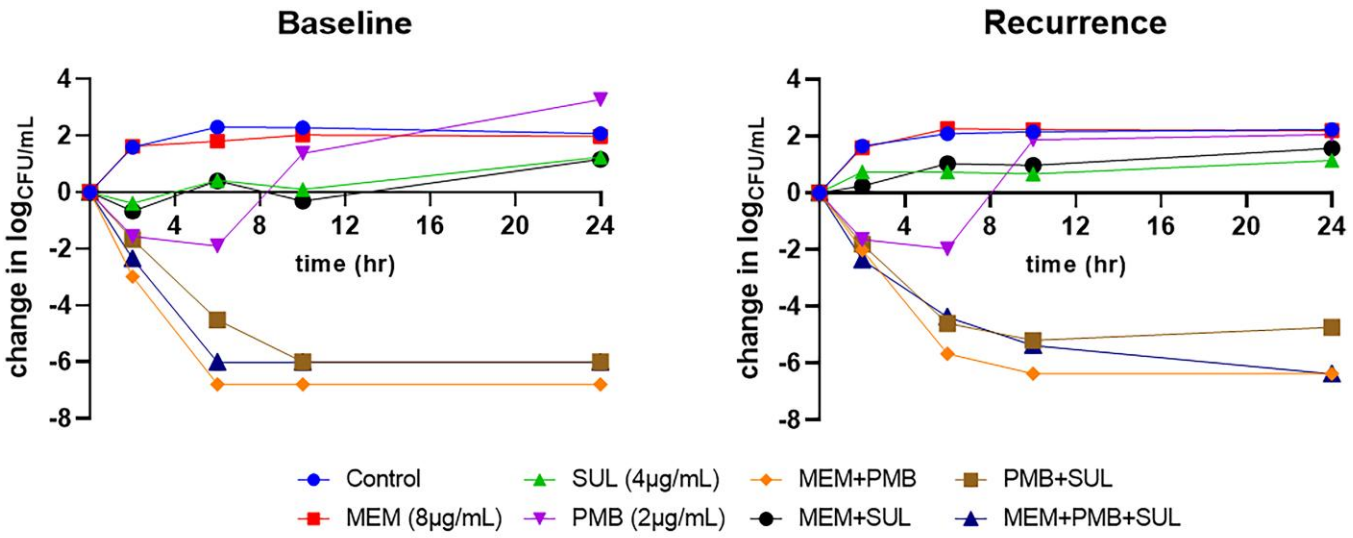
Thirteen representative CRAB isolates from 10 patients underwent WGS. Twelve isolates were collected prior to initial treatment, and one isolate was obtained at the time of recurrent VAP for comparison. All isolates were sequence type (ST) 2 as defined by the Pasteur Institute scheme (^{Pas}) and ST208 by the Oxford scheme (^{Ox}). Isolates varied by ≤2 core genome SNPs suggesting a clonal outbreak at the hospital (Table S2). Each isolate harboured bla_{OXA-66}, $bla_{OXA-24/40}$ and bla_{ADC-30}, and shared the same resistance gene content with one exception (Table S2). No additional mutations in resistance genes were noted, including in *pmrCAB* and *lpxACD* genes that mediate polymyxin resistance.

Eight representative initial CRAB isolates were tested for *in vitro* synergy. Rates of additive or synergistic activity were highest for polymyxin, ampicillin/sulbactam (50%); meropenem, ampicillin/sulbactam (25%); and minocycline, polymyxin b (25%); and <6% for all other combinations (Table 2). In time-kill analyses, initial isolates from three patients were rapidly killed by two-drug combinations of polymyxin b plus meropenem (mean log-kill = −6.29), polymyxin b plus ampicillin/sulbactam (mean log-kill = −5.77), and the three-drug combination of polymyxin b, meropenem and ampicillin/sulbactam (mean log-kill = −5.66). Paired initial and recurrent isolates from one patient (MICU-1) collected before and after 21 days of ampicillin/sulbactam, meropenem, polymyxin b treatment did not demonstrate the emergence of new resistance gene mutations or differences in the killing activity of two- or three-drug combinations (Figure 1).

Discussion

The management of CRAB infections remains a foremost challenge due to limited treatment options and difficulty determining whether poor clinical outcomes are attributable to suboptimal antibiotic therapy or underlying host factors. This paradigm is consistent with the organism's predilection for causing hospital-acquired infections in vulnerable hosts.[7,17] Previous pathogen-focused treatment studies of *Acinetobacter* spp. infections have demonstrated all-cause mortality rates >40%.[4,18,19] Here, we showed the use of potentially synergistic three-drug regimens for severe CRAB infections among critically ill COVID-19 patients that resulted in lower rates of clinical failure and death than those previously reported among non-COVID-19 patients.[18,20]

The most commonly used three-drug regimen at our centre was ampicillin/sulbactam, meropenem and polymyxin b, which demonstrates potent bactericidal activity in dynamic hollow-fibre infection models against CRAB isolates.[6,21] Clinical data, however, are limited to seven patients infected with colistin-resistant CRAB who all survived 30-days post-treatment.[5] Our data, therefore, corroborate and extend prior findings, particularly in support of early initial treatment for severe CRAB infections. Among patients treated with ampicillin/sulbactam, meropenem and polymyxin b, 46% experienced complete resolution of signs and symptoms of infection and the 30-day mortality rate was 23% (3/13). Alternative combinations that have been studied include minocycline, continuous infusion sulbactam and polymyxin B, which also shows rapid killing and minimal development of resistance in a pharmacodynamic model.[8] In our patients, minocycline (200 mg every 12 hours) was used instead of



Minimum inhibitory concentrations (MICs; mg/L) for baseline and recurrence isolates collected from a patient MICU-1 treated with MEM-PMB-SUL for 21 days

Isolate	MEM	PMB	SUL	FDC
Initial	>64	0.25	8	0.25
Recurrent	>64	0.25	16	0.12

Figure 1. Time-kill assays performed for paired initial and recurrent isolates from one patient (MICU-1) collected before and after 21 days of ampicillin-sulbactam, meropenem, and polymyxin b treatment did not demonstrate the emergence of new resistance gene mutations or differences in the killing activity of 2- or 3-drug combinations. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

meropenem in three patients resulting in clinical success in two. All but one patient in our study received polymyxin B as part of combination therapy for which associated outcomes data remain sparse given that most studies have used colistin rather than polymyxin B. Polymyxin B demonstrates pharmacokinetic and safety advantages when compared to colistin, and thus warrants further investigation as part of combination regimens for CRAB infections.[22] Such data may support or refute the frequent use of either colistin or polymyxin B for treatment of carbapenem-resistant Gram-negative bacterial infections among surveyed institutions in the USA and Europe.[23] Motivation for colistin in combination with other agents stems from high rates of *in vitro* synergy; however, *in vitro* synergism against CRAB has not always been associated with improved clinical outcomes.[18,24] A randomized controlled trial of 406 patients with infections due to carbapenem-resistant Gram-negative bacteria, most of which (77%) were caused by *A. baumannii*, did not find a difference in clinical failure rates among patients treated with the combination of meropenem plus colistin versus colistin alone.[18] These findings were corroborated in a second randomized controlled trial of 425 patients where treatment with meropenem plus colistin did not result in improved outcomes compared to colistin alone for patients with CRAB infections.[20]

Patients may have fared better in our study because they received optimized dosing of all antimicrobial agents in combination. For instance, we administered 9 g of ampicillin/sulbactam every 8 hours as a prolonged infusion over 4 hours (equivalent to 3 g every 8 hours of sulbactam), based on pharmacodynamic modelling that shows this regimen achieves a high probability of target attainment for *A. baumannii*.[9,25,26] Other antibiotic regimens were optimized wherever possible, including high-dose, extended infusion meropenem, high-dose minocycline and pharmacokinetically optimized doses of polymyxin B.[6,8] Although we cannot draw definitive conclusions, the ampicillin-sulbactam doses employed here likely achieved pharmacokinetic-pharmacodynamic targets of at least 25% $fT > MIC$ given that sulbactam MICs ranged from 8 to 16 mg/L across all isolates tested.[27,28] These complex regimens are not without risk, however, as 39% of patients experienced antibiotic-associated acute kidney injury probably secondary to polymyxin B. No patients experienced neurotoxicity with the high-dose combinations of beta-lactams and polymyxin B, but our sample size was small.

Taken together, these data bring to the forefront the central challenges in managing CRAB infections, which are frequent microbiologic failures, differentiating recurrent infection versus colonization and the development of further antibiotic resistance

after treatment. CRAB typically affects critically ill patients whose prognosis is influenced by underlying diseases, comorbid conditions, severity of illness and in this report, COVID-19 pneumonia.[29] In our experience with three-drug regimens, microbiologic failures were still common, particularly among patients with VAP. However, increased resistance was not noted among patients with recurrent infection or in circulating isolates associated with the outbreak at our centre. While our *in vitro* findings did not indicate that the three-drug combinations offered superior *in vitro* killing over two-drug combinations, we hypothesize that the addition of a third agent helped to mitigate the emergence of further resistance. By comparison, rates of treatment-emergent colistin resistance ranges from 8% to 36% among patients treated with colistin–meropenem combinations.[20,30] It is unclear whether the propensity for treatment-emergent resistance to colistin differs from polymyxin B.

Another important factor that may have contributed to positive patient outcomes in our study was the early initiation of treatment. Given the nature of the CRAB outbreak, we were able to initiate three-drug combination regimens in 72% of patients within 48 hours of culture collection. This strategy is particularly notable given that delayed time to appropriate antimicrobial therapy is associated with increased mortality in *Acinetobacter* spp. infections.[31,32] It is also possible that treatment responses vary by geographic region and/or CRAB sequence type, which may have impacted findings in this study. Indeed, mortality rates have been shown to vary by CRAB clonal group in previous studies.[33] Here, all patients were infected with closely related $ST2^{Pas}$/$ST208^{Ox}$ isolates and received standardized three-drug regimens. Accordingly, our findings are specific to the clone infecting patients at our centre and underscore the need for future studies that link treatment response to the underlying molecular characteristics of CRAB isolates. These data are particularly important given that the clone causing an outbreak at our institution was universally susceptible to polymyxin B, but minocycline MICs were at or above the susceptibility breakpoint in all cases. Thus, ideal combinations should be tailored to the predominant strain at each institution.

Finally, it should be noted that evaluation of clinical outcomes in this study was limited by the fact that all patients had severe COVID-19 pneumonia. This was problematic in the patients with VAP given the extensive underlying lung damage. For this reason, we conservatively identified those with clinical resolution, and classified other patients as indeterminant if treatment responses could not be clearly ascertained. In addition, we adjudicated outcomes through the independent review of three investigators, which was consistent with the interpretations of treating ID providers. Using this approach, we have shown the potential utility of three-drug regimens for severe CRAB infections among COVID-19 patients that resulted in reasonable rates of clinical response and lower rates of 30-day mortality relative to previous studies. Importantly, the emergence of further antibiotic resistance was not detected phenotypically or through WGS analysis. Given our sample size, we have not correlated individual patient outcomes to infecting isolates that did or did not demonstrate antibiotic synergy. Further studies are needed to link molecular, phenotypic and clinical characteristics with responses to CRAB treatment to elucidate preferred antibiotic combinations, particularly with newer antimicrobial agents such as cefiderocol and with polymyxin-sparing combinations.

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Transparency declarations

Y.D. has served as a consultant for Shionogi, Gilead Sciences, MSD, GSK, Meiji Seika Pharma, Chugai, bioMerieux and has received investigator-initiated funding from Entasis, Shionogi and Asahi Kasei. P.M.L. has served as a consultant for bioMerieux. R.K.S. has served as a consultant for Allergan, Cidara, Shionogi, Menarini, Melinta, Merck, Entasis, Utility and Venatorx and has received investigator-initiated funding from Merck, Melinta, Shionogi and Venatorx. All other authors report no potential conflicts of interest.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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