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NOVEL ID CASES

Novel Combination Therapy for Extensively Drug-Resistant *Acinetobacter baumannii* Necrotizing Pneumonia Complicated by Empyema: A Case Report

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We report our clinical and laboratory experience treating a 50-year-old patient who was critically ill with extensively drug-resistant *Acinetobacter baumannii* necrotizing pneumonia complicated by empyema in Detroit, Michigan. A precision medicine approach using whole-genome sequencing, susceptibility testing, and synergy analysis guided the selection of rational combination antimicrobial therapy.

Keywords. *Acinetobacter baumannii*; combination therapy; antimicrobial resistance; pneumonia; sulbactam–durlobactam.

Acinetobacter baumannii is an urgent threat and critical pathogen for which new antimicrobials are needed [1, 2]. Its numerous intrinsic and acquired resistance mechanisms often render conventional antimicrobials ineffective, leading to the emergence of extensively drug-resistant (XDR) strains, defined as nonsusceptibility to ≥1 agent in all but ≤2 antibiotic categories [3]. Although infections caused by XDR *A. baumannii* continue to increase worldwide, there remain sparse evidence-based data detailing effective therapeutic options. Cefiderocol, Food and Drug Administration (FDA) approved in 2020 for hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) caused by gram-negative susceptible microorganisms including *A. baumannii*, has demonstrated in vitro activity against multidrug-resistant (MDR) *A. baumannii* isolates harboring class D β-lactamases, including OXA-23, OXA-24, OXA-40, OXA-51, and OXA-58 [4]. In contrast, eravacycline, FDA approved in 2018 for complicated intraabdominal infections (cIAIs), has not yet earned an indication specifically for *A. baumannii*, nor has it been assigned a Clinical and Laboratory Standards Institute or FDA breakpoint despite showing in vitro activity against MDR *A. baumannii* isolates [5]. Recently, the investigational drug durlobactam, a potent inhibitor of Ambler class A, C, and D β-lactamases, when used in combination with sulbactam, restored activity of sulbactam against carbapenem-resistant *A. baumannii* isolates [6, 7]. As the incidence of XDR *A. baumannii* isolates increases, health care teams are gaining experience with these agents as monotherapy and in combination with traditional antimicrobials to explore their place in therapy.

CASE PRESENTATION

A 50-year-old man presented to an affiliate hospital with chest pain and shortness of breath. Chest computed tomography (CT) showed pulmonary emboli throughout the left lower segmental arteries and right lower lobe (RLL) with progression of previously seen pulmonary infarction. On hospital day 6, the patient transferred in as an intensive care unit direct admission and was intubated for severe respiratory distress. The next day, his repeat CT showed progressive necrosis of the RLL infarction, and he underwent a thoracotomy with partial decortication and right thoracoscopy with 3 chest tubes placed and was started on empiric piperacillin-tazobactam and intravenous (IV) vancomycin (Figure 1). A bronchoalveolar lavage on hospital day 9 resulted positive for meropenem-susceptible *A. baumannii* on hospital day 12, so antibiotics were switched to 3-hour extended infusion meropenem. Also, on hospital day 12, the patient underwent another thoracotomy with RLL resection and complete decortication due to a new large multiloculated pleural effusion. Pathology of the pleural peel demonstrated acute fibrinopurulent exudate, and the resected RLL demonstrated extensive abscess, necrosis, and hemorrhage. Pleural tissue culture demonstrated XDR *A. baumannii* on hospital day 18, with intermediate susceptibility to colistin (minimum inhibitory concentration [MIC], 0.5 mg/L) and a tigecycline MIC of 2 mg/L (Figure 1), which prompted the switch from meropenem to tigecycline 100 mg every 12 hours on hospital day 19 [3]. On hospital day 26, after a week of tigecycline monotherapy, the patient required vasoactive agents and his CT chest demonstrated RLL pyopneumothorax, so tigecycline was switched to colistin 150 mg IV every 12 hours and meropenem infused over 3 hours. Due to persistent purulent chest tube drainage, the patient underwent a bronchoscopy on hospital day 28, which

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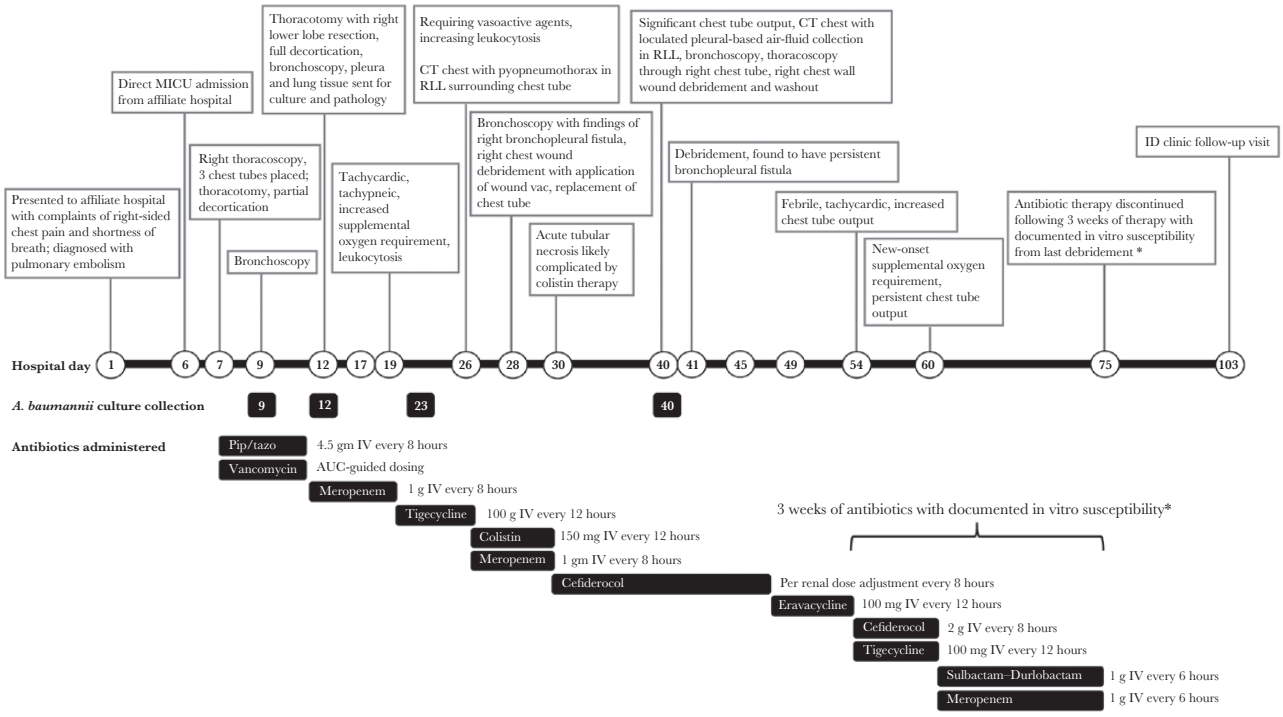

Positive *A. baumannii* cultures		MIC, mg/L									
Day	Specimen	AMK	AMP-SUL	TIG	MEM	MIN	COL	ERV	FDC	SD	SD+ MEM
9	Aspirate bronchoscopy	>32	2/1	2	≤0.25	8	N/A	N/A	N/A	N/A	N/A
12	Tissue right pleura	>32	64[a]	2[a]	>32[a]	8[a]	0.5[a]	N/A	N/A	N/A	N/A
23	Right chest tube fluid	>32	>16/8	4	>8	8	0.5	0.5[a]	0.5	N/A	N/A
40	Sputum bronchus wash	>32	>16/8	4	>8	8	0.5	1[a]	>16	8[b]	4[b]

Figure 1. Timeline of hospital encounter and *Acinetobacter baumannii* isolate susceptibility data. Nonsusceptible MIC values and MIC values for which there are no established Clinical and Laboratory Standards Institute breakpoints (eg, TIG, ERV) are in shaded table boxes [16, 17]. [a]Determined by e-test. [b]Based on SUL-DUR preliminary susceptibility breakpoint (4 mg/L). *Documented in vitro susceptibility based on current and previous data in XDR *A. baumannii* isolates [8]. Abbreviations: AMK, amikacin; AMP-SUL, ampicillin-sulbactam; COL, colistin; CT, computed tomography; CXR, chest X-ray; ERV, eravacycline; FDC, cefiderocol; I, intermediate; ID, infectious diseases; IV, intravenous; MEM, meropenem; MICU, medical intensive care unit; MIN, minocycline; N/A, not available; pip/tazo, piperacillin/tazobactam; R, resistant; RLL, right lower lobe; S, sensitive; SD, sulbactam–durlobactam; TIG, tigecycline; U, unknown breakpoint for *A. baumannii*; XDR, extensively drug-resistant.

identified a right bronchopleural fistula. Additionally, the patient experienced acute tubular necrosis with serum creatinine increasing 7-fold from baseline, from 1.10 to 7.60, which, although likely multifactorial, may have been complicated by colistin therapy. For these reasons, the infectious diseases (ID) service requested eravacycline and cefiderocol susceptibilities on the chest tube fluid culture from hospital day 23, which resulted susceptible with an MIC of 0.5 mg/L for cefiderocol via broth microdilution and 0.5 mg/L for eravacycline via E-test (no eravacycline breakpoint available for *A. baumannii*) on hospital day 29, so colistin and meropenem were switched to renally adjusted cefiderocol. Significant chest tube output continued with an average of 225 mL per day. Out of concern for an unresolving infection, bronchial washings were collected for culture on hospital day 40, which resulted positive for XDR *A. baumannii* on hospital day 45. The *A. baumannii* isolate was determined to be cefiderocol-resistant (zone diameter ≤11 mm) per disk diffusion testing, so cefiderocol was switched to eravacycline 1 mg/kg on hospital day 49 based on its MIC of 0.5 mg/L from the previous culture. On hospital day 54, the patient was febrile and tachycardic and had increased chest tube output, and the eravacycline E-test MIC increased to 1 mg/L, so eravacycline was discontinued and combination therapy with cefiderocol 2 g every 8 hours and tigecycline 100 mg every 12 hours was initiated based on published in vitro data demonstrating synergy against 6/6 MDR *A. baumannii* isolates [8]. While the patient received combination therapy, chest tube output remained persistent, so ID requested susceptibility testing for sulbactam–durlobactam (SUL-DUR), which is available through an expanded access program for MDR *A. baumannii* infections. The SUL-DUR MIC was 8 mg/L, 1 dilution above the preliminary susceptibility breakpoint (4 mg/L); however, the addition of meropenem reduced the MIC to 4 mg/L, as determined by the institution via broth microdilution.

With data demonstrating in vitro susceptibility to SUL-DUR plus meropenem, cefiderocol and tigecycline combination therapy was discontinued, and 1 g sulbactam/1 g durlobactam every 6 hours plus meropenem 1 g every 6 hours was started per the manufacturer's protocol on hospital day 62 due to the patient's increased supplemental oxygen requirement and persistent chest tube output. On hospital day 75, after 13 days of SUL-DUR and meropenem and resolution of chest tube output, the patient completed 3 weeks of antibiotic therapy with documented in vitro susceptibility from the last debridement, with no reported adverse drug effects [8]. Antibiotics were discontinued, and 2 days later he was cleared for discharge. The patient followed up with ID as an outpatient and 4 weeks later was at his prehospital baseline.

For all XDR *A. baumannii* isolates, chromosomal DNA extraction, whole-genome sequencing (WGS), and genomic content analysis were performed at Entasis Therapeutics. Full methods and accession numbers are provided in the Supplementary Data. Isolates underwent sequence analysis of known antibiotic resistance genes. All 3 tested patient isolates (collected on hospital days 12, 23, 40) encoded resistance genes for aminoglycosides, fluoroquinolones, macrolides, sulfonamides, and tetracyclines, plus 2 Class D and 1 Class C carbapenemase genes: OXA-23, OXA-66, and *Acinetobacter*-derived cephalosporinase (ADC)-30. The OXA-23 carbapenemase is a type of acquired resistance, whereas OXA-66 and AmpC β-lactamases are intrinsic mechanisms that confer carbapenem and cephalosporin resistance, respectively [9]. The cefiderocol-resistant isolate revealed a mutation in the TonB-dependent siderophore receptor (A1S_0980) [K628], which was likely the source of cefiderocol resistance. Full WGS results are provided in the Supplementary Data.

Checkerboard assays, combination MICs, and time-kill analyses (TKA) were used to explore potential synergistic effects of SUL-DUR in combination with meropenem for *A. baumannii* against the cefiderocol-resistant isolate. Meropenem powder was purchased commercially from Sigma Chemical Company (St. Louis, MO, USA), and SUL-DUR powder was provided by the manufacturer, Entasis Therapeutics (Waltham, MA, USA). All in vitro analyses were performed following Clinical Laboratory Standards Institute (CLSI) guidelines [10]. Combination MIC testing with SUL-DUR (durlobactam 4 mg/L kept constant) in the presence of subinhibitory amounts of meropenem (0.5 × MIC of meropenem) was performed, as was meropenem in the presence of subinhibitory amounts of SUL-DUR (0.5 × MIC of SUL-DUR) [11]. Combination MIC testing revealed a 4-fold meropenem MIC reduction in the presence of SUL-DUR (MIC 64 to 16) and a 2-fold SUL-DUR MIC reduction in the presence of meropenem (MIC 8 to 4).

The isolate was further evaluated for SUL-DUR and meropenem synergy by checkerboard analysis in duplicate (using durlobactam 4 mg/L kept constant). Synergy was defined as a fractional inhibitory concentration (FIC) index ≤0.5 [12]. The FIC index considers the combination of antibiotics that produces the greatest change from the individual MIC. The checkerboard assay revealed SUL-DUR and meropenem synergy with FIC = 0.375 (Figure 2A).

TKAs were performed using inocula obtained from stationary phase cultures and 2 replicates obtained at each time point, according to CLSI standards [13]. Antimicrobials were tested at their respective synergistic concentrations as determined by checkerboard analysis or maximum concentration of free drug in serum (*f*Cmax) [14, 15]. Sulbactam and durlobactam concentrations were kept at a 1:1 ratio (ie, 2/2 mg/L) to mimic the proposed dosing regimen. Synergy was defined as a >2 $\log_{10}$ CFU/mL reduction over the most potent single agent. Against the XDR *A. baumannii,* SUL-DUR plus meropenem was synergistic (Figure 2B), which may have contributed to the successful treatment of this patient.

DISCUSSION

The treatment of XDR *A. baumannii* remains challenging due to its propensity to confer multiple resistance mechanisms and sparse clinical data evaluating potentially effective therapeutic options, including the novel agents eravacycline, cefiderocol, and sulbactam–durlobactam, as monotherapy or in combination with conventional antimicrobials.

While phase 3 trials have demonstrated the efficacy of eravacycline in cIAIs caused by *Enterobacterales*, limited information exists for *A. baumannii* infections. Pharmacodynamic/pharmacokinetic (PK/PD) evaluations of eravacycline in *Enterobacterales* have identified *f*AUC/MIC targets for stasis and 1-log-kill end points of 27.97 ± 8.29 and 32.60 ± 10.85, respectively [16]. However, the European Medicines Agency (EMA) assessment report for eravacycline suggests that *f*AUC/MIC targets would not be achieved in *Enterobacterales* with MICs >0.12 [17]. Therefore, it is especially difficult to interpret the patient isolate eravacycline MICs given the lack of efficacy outcome data and PK/PD analyses for *A. baumannii* infections. Eravacycline MICs are, in general, 2-fold lower than those of tigecycline against carbapenem-resistant *A. baumannii* isolates. Additionally, eravacycline remains active against isolates harboring tetracycline efflux pump genes and is reliable against OXA carbapenemases and colistin-resistant isolates [18]. However, clinical trial data evaluating the efficacy of eravacycline against MDR *A. baumannii* isolates are limited to data from phase 3 cIAI and complicated urinary tract infection (cUTI) trials [19, 20]. For cIAIs, eravacycline was noninferior to ertapenem and meropenem, but only 3% and 2% of those patients had *A. baummannii* infections, respectively. For cUTI, eravacycline was inferior to levofloxacin and meropenem.

Cefiderocol has demonstrated in vitro activity against >95% of meropenem-nonsusceptible *A. baumannii* isolates harboring class D β-lactamases per surveillance data using

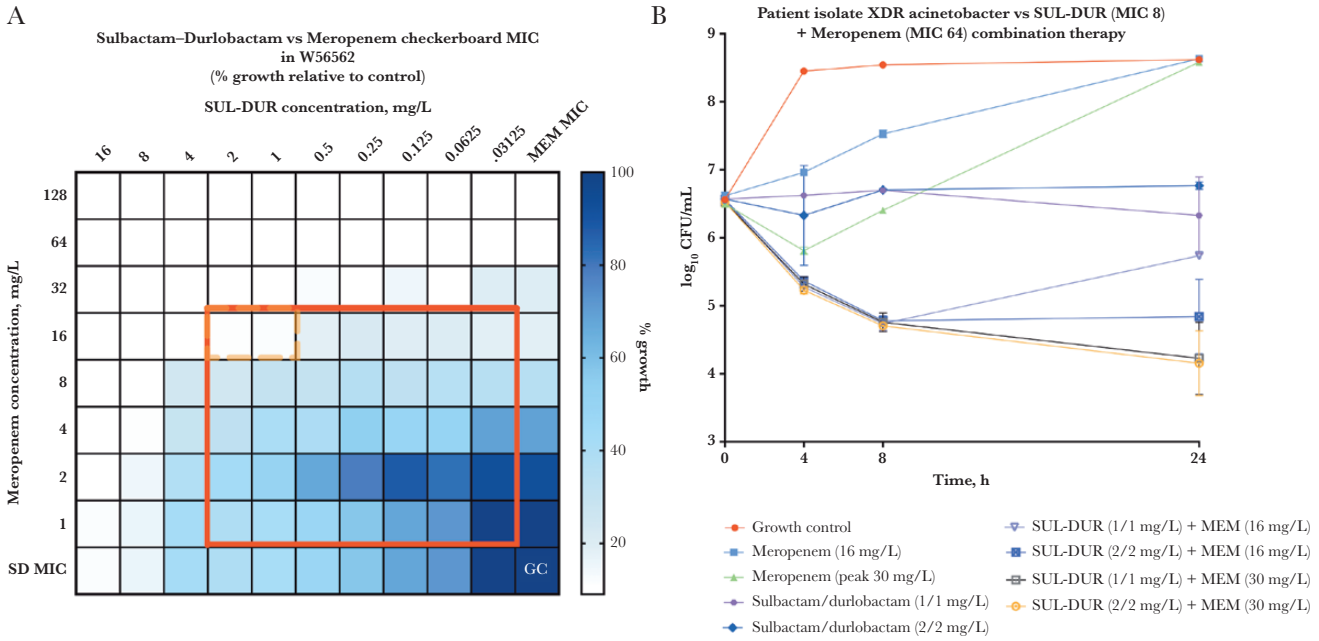

Figure 2. A, Checkerboard analysis for synergy. Columns 1–10 contain 2-fold serial dilutions of SUL-DUR, and rows 1 to 8 contain 2-fold serial dilutions of MEM. The results are used to calculate the FIC value and then assessed for synergism, additive/indifference, or antagonism. In this illustration, "no growth" is represented by white squares and "growth" is represented by blue squares, with increasing darkness representative of higher CFU/mL. The red outline represents the area for potential synergy (FIC ≤0.5). The orange dotted outline represents the area of a demonstrated synergistic effect (FIC ≤0.5) between SUL-DUR and meropenem. B, Time-kill analysis. Planktonic time kill analyses for XDR *A. baumannii* patient isolate against combination therapy with sulbactam-durlobactam plus meropenem. The addition of meropenem (30 mg/L) to SUL-DUR (1 mg/L and 2 mg/L) demonstrates a synergistic effect. Abbreviations: CFU, colony-forming units; GC, growth control; MEM, meropenem; MIC, minimum inhibitory concentration; SUL-DUR, sulbactam–durlobactam; XDR, extensively-drug resistant.

CLSI susceptibility criteria ≤4 mg/L [21]. However, similar to eravacycline, clinical data supporting its use for infections caused by MDR *A. baumannii* are limited to 2 phase 3 trials. CREDIBLE-CR enrolled 54 patients with infections due to carbapenem-resistant gram-negative bacteria. While clinical cure rates were similar between cefiderocol and the best available therapy (mostly composed of polymyxin-based regimens), patients who received cefiderocol had increased all-cause mortality, which was driven by higher mortality in patients with *A. baumannii* infections [22]. APEKS-NP enrolled 300 critically ill patients with nosocomial pneumonia and identified no difference in 14-day all-cause mortality between cefiderocol and optimized meropenem (2 g IV every 8 hours, 3-hour extended infusion). Notably, 16% of those enrolled were infected with *A. baumannii*, of whom 66% were carbapenem-resistant [23].

Durlobactam has demonstrated in vitro activity against Ambler class A, C, and D β-lactamases [24]. One study reported the in vitro activity of SUL-DUR against 1722 clinical isolates of the ABC complex (*A. baumannii*, *Acinetobacter calcoaceticus, Acinetobacter nosocomialis*, and *Acinetobacter pittii*) collected globally in 2016 and 2017 [7]. Of the isolates tested, 97.7% had an SUL-DUR MIC of ≤4 μg/mL, the proposed SUL-DUR breakpoint, which is based on preclinical and clinical modeling of joint PK/PD target attainment analysis for sulbactam and durlobactam [25–27]. Among the SUL-DUR-nonsusceptible isolates (2.3%), most encoded either the NDM-1 metallo β-lactamase, which is not inhibited by durlobactam, or amino acid changes in PBP3, the target of sulbactam [7]. Given this information, it is reasonable to conclude that for *A. baumannii* isolates with MIC >4 μg/mL, the addition of a carbapenem to SUL-DUR therapy may be an alternative therapeutic choice, although additional studies are warranted.

Results were recently released from ATTACK, a global phase 3 registration trial evaluating the safety and efficacy of SUL-DUR for the treatment of carbapenem-resistant *A. baumannii* HABP, VABP, or bacteremia. In the study, patients were randomized to receive either SUL-DUR (dosed 1 g/1 g infused over 3 hours) or colistin (2.5 mg/kg infused over 30 minutes every 12 hours), both in combination with imipenem/cilastatin. In total, 207 patients were enrolled from 95 clinical sites across 17 countries. SUL-DUR met the primary end point of 28-day all-cause mortality showing noninferiority compared with colistin in a microbiologically modified intent-to-treat population, with a statistical trend toward lower mortality among patients who received SUL-DUR vs colistin (19% [12/63] vs 32.3% [20/62], respectively). Additionally, clinical response at test-of-cure once again favored SUL-DUR with 61.9% compared with 40.3% in the colistin arm. The study's primary safety objective was also met with a significant reduction in nephrotoxicity among patients who received at least 1 dose of SUL-DUR or colistin (13.2% [12/91] vs/ 37.6% [32/85], respectively; ClinicalTrials.gov NCT03894046: http://clinicaltrials.gov/

ct2/show/NCT03894046 [28]. While the use of combination therapy in this study aligns with the newly published Infectious Diseases Society of America guidance for the treatment of moderate to severe infections caused by carbapenem-resistant *A. baumannii*, it leaves in question the optimal combination agents to be used with SUL-DUR [29].

To our knowledge, this is the first case report documenting SUL-DUR plus meropenem combination therapy as an adjuvant to surgical management for necrotizing XDR *A. baumannii* pneumonia complicated by empyema. The addition of meropenem to SUL-DUR in this case instead of imipenem–cilastatin was secondary to institutional formulary restrictions. Further in vitro analyses revealed synergistic effects with SUL-DUR plus meropenem against the third XDR patient isolate, which may have contributed to the patient's resolution of chest tube output. However, without safety and efficacy data from clinical trials, it is difficult to assess the role of meropenem as a combination agent with SUL-DUR in the successful treatment of this patient. The positive impact of this combination may also in part be due to durlobactam's unique ability to restore sulbactam activity against MDR *A. baumannii*. A similar case report described combination SUL-DUR and cefiderocol therapy for the treatment of XDR *A. baumannii* in a patient with severe COVID-19 and septic shock secondary to HABP [30].

CONCLUSIONS

This case describes the clinical use of combination 1 g sulbactam/1 g durlobactam every 6 hours as a 3-hour infusion with meropenem 1 g every 6 hours administered via 30-minute infusion for necrotizing XDR *A. baumannii* pneumonia/empyema. The resultant in vitro synergy of this combination may have contributed to the successful treatment of this patient. Thus, in patients with XDR *A. baumannii* demonstrating in vitro resistance to SUL-DUR, combination therapy of SUL-DUR with meropenem may be an appropriate therapy option. Additional clinical trials are necessary to inform use of SUL-DUR both as monotherapy and in combination with conventional antimicrobial therapies pending its approval for use in *Acinetobacter* infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This study does not include factors necessitating patient consent.

Data availability. Data are available at GenBank accession numbers JAJKGU000000000, JAJKGT000000000, and JAJKGS000000000. Full WGS methods and results are provided in the Supplementary Data.

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