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CASE REPORT

Combination Therapy for OXA-48 Carbapenemase-Producing *Klebsiella Pneumoniae* Bloodstream Infections in Premature Infant: A Case Report and Literature Review

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Abstract: The prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has been increasing in recent years. Chinese Infectious Disease Surveillance of Pediatrics (ISPED) showed that in 2022, its resistance rate to meropenem was 18.5%. However, there is limited data available on the treatment of CRKP infection in neonates. In this study, we present a case involving a premature infant infected with OXA-48-producing *Klebsiella pneumoniae*. The combined susceptibility test revealed a significant synergistic effect between ceftazidime–avibactam(CAZ-AVI), and aztreonam(ATM). The infection was successfully treated with a combination of CAZ-AVI, ATM, and fosfomycin. This case represents the first reported instance of sepsis in a premature infant caused by OXA-48-producing *Klebsiella pneumoniae* in China. The objective of our study is to evaluate the effectiveness and safety of combination therapy in treating CRKP infections in premature infants. We hope that the findings of this study will provide valuable insights for clinicians in their treatment approach.

Keywords: OXA-48, *Klebsiella pneumoniae*, premature infant, ceftazidime–avibactam, aztreonam

Introduction

Carbapenem-resistant Enterobacteriaceae (CRE) infections have gradually become the global concerns. *Klebsiella pneumoniae* is an opportunistic pathogen, a non-motile, and encapsulated gram-negative bacilli of the Enterobacteriaceae.[1] It is the main cause of neonatal sepsis in low-income countries (LICs) and lower-middle-income countries (LMICs).[2] In recent years, the prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has increased, and the emergence of carbapenem-resistant hypervirulent *Klebsiella pneumoniae* poses a huge threat to human public health.[3,4] The global prevalence of CRKP among patients with KP infections was estimated to be 28.69%, and the prevalence rate of the CRKP vary greatly by country and region.[5] According to the statistics of China Antimicrobial Surveillance Network (CHINET), *Klebsiella pneumoniae* ranked second in the clinical isolates in China, and the resistance rate to meropenem has increased to 26.0% in 2023.[6] A systematic review estimated that there could be at least 60,000 cases of CRKP infections and 5880 deaths in neonates worldwide.[7] CRKP showed a high resistance rate to many clinical antibiotics, which limited antimicrobial treatment options.

Especially in the special population of premature infants, who are hospitalized for a long time and need for invasive procedures, which place them at great risk of infections.[8] Studies have shown that premature, low-birth-weight and presence of an indwelling central vascular catheter are common risk factors for neonatal sepsis.[8,9] A systematic review of 128 articles across 30 countries found that, the pooled prevalence of CRKP infection in hospitalized newborns was 0.3%

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in LICs and LMICs, and was significantly higher in NICU than in non-ICU neonatal care unit.[7] In China, the separation rate of CRKP in neonates decreased year by year from 2016 to 2020, but it was still higher in the neonatal group than in the nonneonatal group.[10] This also suggests that CRKP post more threat to newborns.

Antibacterial agents reported in current studies for CRE include Ceftazidime-avibactam (CAZ-AVI), colistin, fosfomycin, cefiderocol, tigecycline and eravacycline, etc.[11–13] The Infectious Diseases Society of America suggested that CAZ-AVI is the preferred treatment option for OXA-48-like producing infections.[14]

CAZ-AVI is a new third-generation cephalosporin/beta-lactamase inhibitor combination, which has good in vitro activity against Enterobacteriaceae.[15,16] Avibactam protects ceftazidime from Ambler class A (eg, KPC-2), class C (eg, AmpC), and specific class D beta-lactamases (eg, OXA-48), but has no activity against class B enzymes (metallo-beta-lactamases).[17,18] In 2019, FDA approved CAZ-AVI for complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired bacterial pneumonia and ventilator-associated bacterial by designated susceptible Gram-negative microorganisms in adult and pediatric patients aged 3 months and older. Unfortunately, it is not yet approved for neonates and preterm infants. Only a few case reports and case series mentioned the use of CAZ-AVI in premature infants. The safety and efficacy of CAZ-AVI in premature infants have not been established.

Herein, we describe a case of a premature infant infected with ESBL- and OXA-48-producing *Klebsiella pneumoniae*, successful treatment with CAZ-AVI, aztreonam (ATM) and fosfomycin. And we review the literature for 23 premature infants who infected with CRKP.

Case Report

The premature neonate was delivered via cesarean section to a 34-year-old mother who had a diagnosed scarred uterus, chronic hypertension with preeclampsia, subclinical hyperthyroidism, and chronic fetal distress during pregnancy. The neonate was the younger of twins, born at 32 weeks gestation with a weight of 1370g. Apgar scores at 1, 5, and 10 minutes after initial resuscitation and positive airway pressure were recorded as 9, 10, and 10 respectively. The infant was subsequently diagnosed with prematurity, very low birth weight status, and neonatal respiratory distress syndrome (NRDS), and was admitted to the neonatology department for T-piece ventilation support. The twin brother weighed 1630g at birth and had good overall health. He remained hospitalized for twenty-one days without requiring antibiotic treatment.

As per the institutional protocol, a pulmonary surfactant was administered upon admission, followed by caffeine citrate. The infant was breastfed with 2mL of milk every 3 hours. However, the infant repeatedly experienced retention of grass green matter, abdominal distension, and required additional nutrition through a peripherally inserted central catheter (PICC) for intravenous feeding. To mitigate the risk of infection, ampicillin-sulbactam (ampicillin 50mg/kg IV q12h, in a 2:1 ratio) was administered starting on day 3. After completing the treatment, ampicillin-sulbactam was discontinued on day 13. Subsequently, the patient underwent successful extubation and was transitioned to noninvasive ventilation. However, on day 19, the patient experienced sudden fever (Figure 1), decreased pulse oxygen, accelerated heart rate and respiration, decreased blood pressure, cyanosis, and body speckle. C-reactive protein (CRP) (Figure 1) was measured at 30.14mg/L and procalcitonin (PCT) at 3.41ng/mL. Considering the possibility of neonatal sepsis and septic shock, empirical anti-infective therapy was initiated using meropenem (20mg/kg IV q8h). At the same time, blood cultures were obtained, and a lumbar puncture was performed.

On day 23, a blood culture revealed the presence of multidrug-resistant *Klebsiella pneumoniae* (Figure 2). The drug susceptibility results indicated that the bacterium was sensitive to tigecycline, amikacin, gentamicin, and tobramycin, and showed an intermediate response to cefoperazone-sulbactam (Table 1). Consequently, cefoperazone-sulbactam (30mg/kg IV q8h, in a 1:1 ratio) and amikacin (7.5mg/kg IV q12h) were administered instead. However, over the next two days, the patient's body temperature remained at 38°C, CRP levels increased to 172.17mg/L, and the infection symptoms did not improve. Subsequently, we conducted in vitro rapid carbapenemase type detection and combined drug susceptibility testing (Figure 3), which revealed that the bacterium primarily produced ESBL and OXA-48 carbapenemase. Furthermore, in vitro testing demonstrated synergistic effects of CAZ-AVI + ATM. Therefore, a combination of ATM (30 mg/kg IV q8h) and CAZ-AVI (62.5 mg/kg IV q8h) was administered instead.

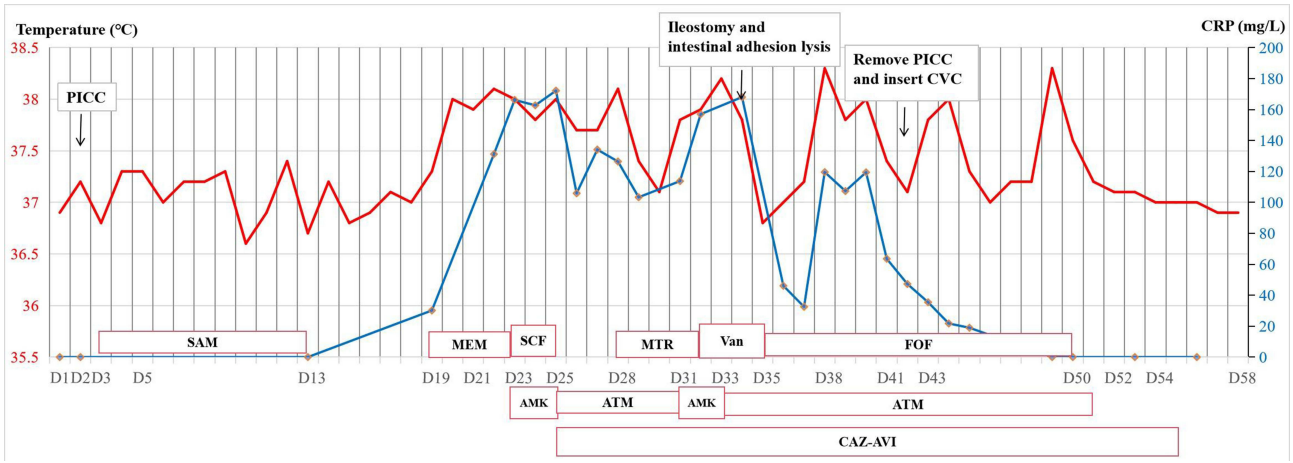

Figure 1 Changes in temperature and CRP of the patient during hospitalization and the changes of antimicrobial agents.
Abbreviations: SAM, ampicillin-sulbactam; MEM, meropenem; SCF, cefoperazone-sulbactam; MTR, metronidazole; Van, vancomycin; FOF, fosfomycin; AMK, amikacin; ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam.

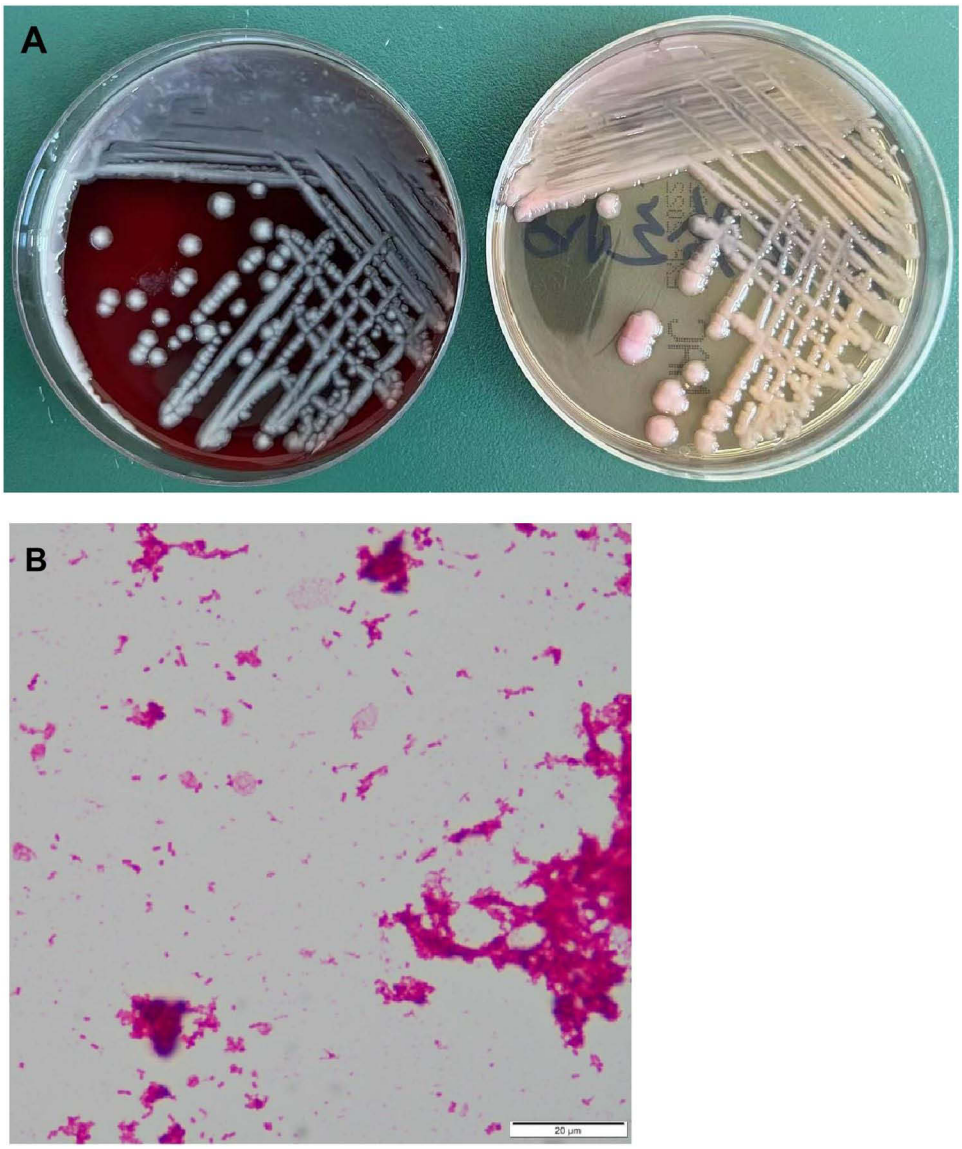

Figure 2 Aetiological examination of multidrug-resistant *Klebsiella pneumoniae*: (**A**) colonies; (**B**) Gram stain.

Table 1 Antimicrobial Susceptibility of Multidrug-Resistant Klebsiella Pneumoniae

Antibiotics	MIC (mg/mL)	KB (mm)	Interpretation
Levofloxacin	≥8.0		R
Tigecycline	2.0		S
ESBL	Pos		Pos
Cefazolin	≥64.0		R
Ceftriaxone	≥64.0		R
Amoxicillin-clavulanate	≥32.0		R
Piperacillin-tazobactam	≥128.0		R
Cefepime		15	R
Aztreonam	16.0		R
Ertapenem	≥8.0		R
Imipenem	4.0		R
Amikacin	<=2.0		S
Gentamicin	<=1.0		S
Tobramycin	<=1.0		S
Ciprofloxacin	≥4.0		R
TMP-SMZ	≥320.0		R
Cefuroxime		6	R
Cefoperazone-sulbactam		16	I
Meropenem		15	R

Abbreviations: MIC, minimum inhibitory concentration; KB, Kirby-Bauer disc diffusion method; mm, millimeter; R, resistance; S, susceptibility; Pos, positive; TMP-SMZ, Trimethoprim-sulfamethoxazole; I, intermediate susceptibility.

On day 31, the patient's temperature increased again to 37.8°C and the levels of PCT increased to 15.9 ng/mL, while the platelet count continued to decrease to 10.1×10^9/L. As a result, the patient's antimicrobial therapy was changed to amikacin (7.5mg/kg IV q12h). However, the patient's condition worsened again the following day, leading to the administration of vancomycin (10mg/kg IV q6h) empirically. Simultaneously, blood culture and metagenomics next-generation sequencing (mNGS) were performed (Table 2 and Figure 4). At present, the patient's anti-infection plan consists of CAZ-AVI, amikacin, and vancomycin.

On day 33, the patient's temperature remained high at 38.2°C, and there was an increase in abdominal bloating. Due to the PICC being in place for over 1 month, fluconazole (4.5mg/kg IV biw) was added to prevent fungal infection. On day 34 after admission, the ultrasound revealed slowed peristalsis, gas accumulation in the intestinal wall, and ascites. The diagnosis of necrotizing enterocolitis (NEC) was confirmed, leading to the performance of ileostomy and enterolysis. The mNGS also detected blaOXA-48 *Klebsiella pneumoniae*. Consequently, we recommended switching amikacin back to ATM (30mg/kg IV q6h) and continuing the combination of CAZ-AVI for treatment. Vancomycin was discontinued and replaced with fosfomycin (33mg/kg IV q8h). The current anti-infection plan consists of CAZ-AVI + ATM + fosfomycin + fluconazole. With this treatment plan, the patient's temperature returned to normal and the CRP decreased to 32.52mg/L.

On the 38th day, the patient experienced another episode of fever with a body temperature of 38.3°C and an increase in CRP to 119.54 mg/L. Considering the prolonged presence of the PICC for over a month and the potential risk of catheter-related infection, a central venous catheter (CVC) was inserted on the 42nd day. Simultaneously, the PICC was removed, and the fistula tract was cleaned and the fistula bag replaced. Following these interventions, the patient's body temperature remained stable compared to before, and symptoms such as shortness of breath, groaning, and cyanosis gradually improved. Additionally, the inflammatory markers gradually decreased, and all three subsequent blood cultures were negative. Subsequently, we gradually discontinued the administration of fosfomycin, ATM, CAZ-AVI, and fluconazole in sequential order. The patient was discharged after achieving a stable condition, resulting in a total

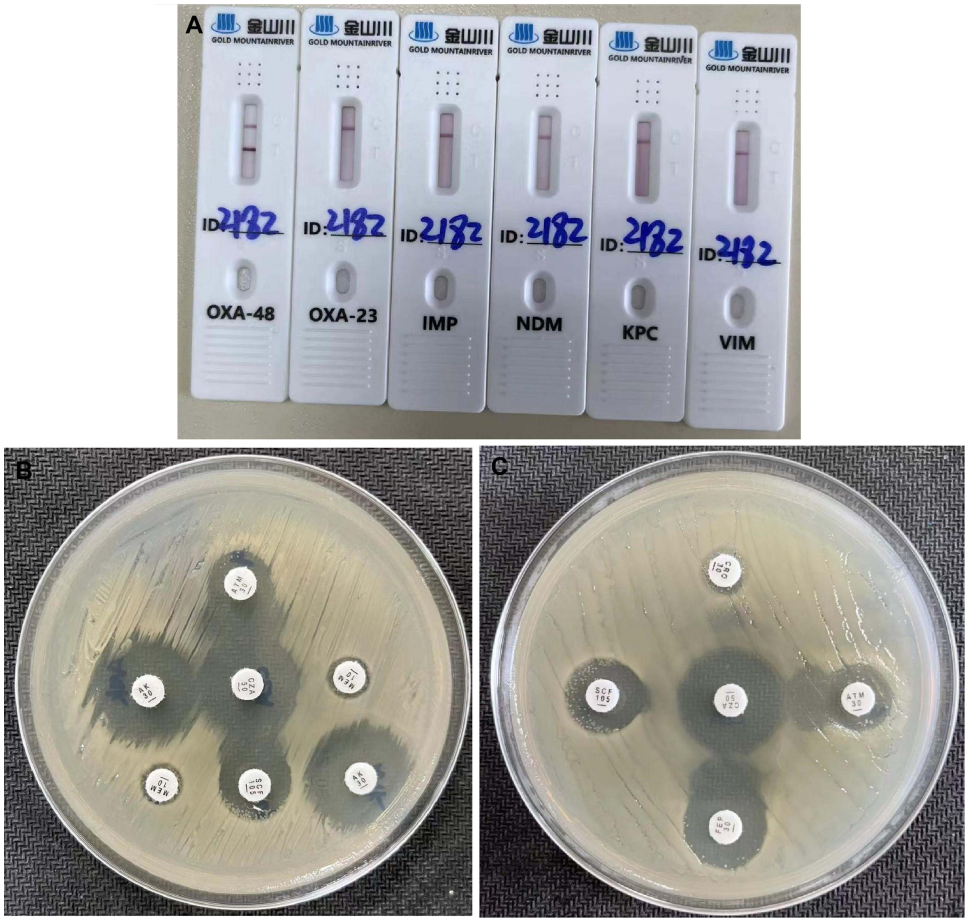

Figure 3 Rapid enzyme type detection (**A**) and combination susceptibility test in vitro (**B** and C).
Abbreviations: ATM, aztreonam; AK, amikacin; CZA, ceftazidime-avibactam; MEM, meropenem; SCF, cefoperazone-sulbactam; CRO, ceftriaxone; FEP, cefepime.

hospitalization period of 58 days. No adverse effects that could be attributed to the combined therapy were observed during the treatment.

Literature Review

PubMed and Embase were searched for relevant studies, combining Medical Subject Heading (MeSH) and free-text terms for "Infant, Premature" and "Klebsiella pneumoniae". Finally, 14 articles and 23 patients were selected.[17,19–31]

Table 3 presents a summary of the 24 premature infants, including the case discussed in this study. Our findings indicate a high failure rate when using meropenem alone or in combination with aminoglycosides or polymyxins to treat severe CRE infections. Among these cases, 13 children opted for CAZ-AVI as a salvage therapy after not responding to initial treatment. Remarkably, all patients except one were successfully cured. The one patient who died had negative blood cultures on the fourth day of CAZ-AVI treatment, but the cause of death was likely attributed to other factors such as premature birth and/or chronic lung disease. In conclusion, based on our analysis of published cases, CAZ-AVI-based regimens can be considered as an alternative treatment option when initial treatment fails.

Table 2 mNGS Results of Blood Culture

Name of Pathogen	Reads Per Ten Million	Genus Name	Relative Abundance (%)	Resistance Gene Name
Klebsiella pneumoniae	120,540	Klebsiella	81.2	blaOXA-48

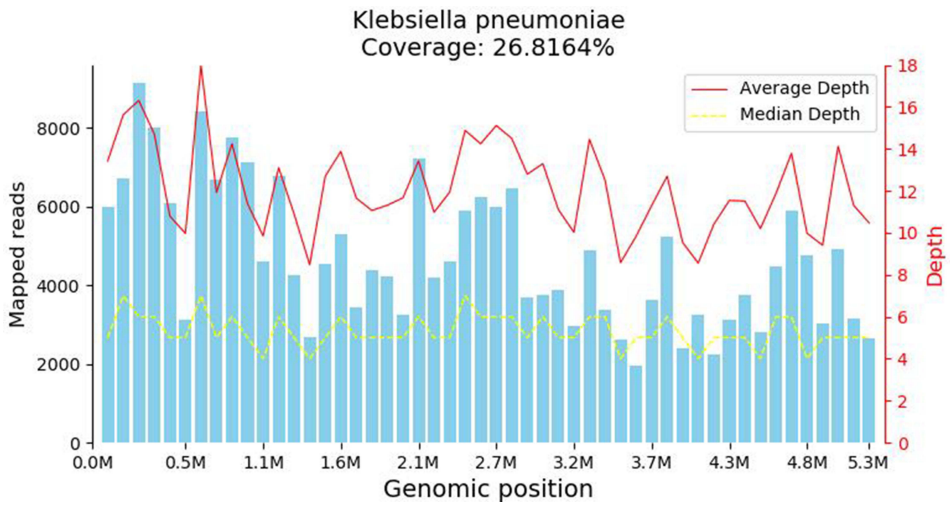

Figure 4 mNGS Results of blood culture.

Discussion

The infection data of Chinese children collected by the Infectious Disease Surveillance of Pediatrics (ISPED) in recent years showed that the detectable rate of *Klebsiella pneumoniae* in neonates and the resistance rate of meropenem decreased slightly in 2020 and 2021 due to the COVID-19, but there is a trend of recovery.[32,33] *Klebsiella pneumoniae* of newborns in China accounted for the third clinically isolated bacteria (12.6%), and its resistance rate to meropenem was 18.5%. *Klebsiella pneumoniae* producing ESBL accounted for 42.3%.[34] A study from the Children's Hospital in Shanghai, China, suggested that the detection rate of OXA-48 in CRE strains in children was 0.7.[35] Unfortunately, we did not find a report on the national epidemiology of OXA-48 in children in China.

The infection in this case is caused by OXA-48-producing *Klebsiella pneumoniae*. Current studies suggest that the progenitors of the blaOXA-48-like genes are the waterborne, environmental and non-human-pathogenic *Shewanella* spp., and the *Serratia marcescens* could have played the role of intermediate reservoir.[36,37] The current transmission of blaOXA-48 gene is mainly related to the dissemination of a single IncL/ M-type self-transfer plasmid of 62 kb.[38–40] OXA-48 is an Ambler class D beta-lactamase, which has the ability to hydrolyze carbapenems. However, its enzyme activity can be inhibited by avibactam.[41] Studies have shown that OXA-48 is closely associated with extended-spectrum beta-lactamases (ESBLs).[16] In a recent study, it was found that 69% of the 113 OXA-48-producing isolates also produced ESBLs.[42]

A retrospective cohort study conducted in 2017 found that patients with bloodstream infections (BSIs) caused by carbapenemase-producing Enterobacteriaceae (CPE) had a lower mortality rate when treated with combination therapy rather than monotherapy.[43,44] In previous case reports involving premature infants, carbapenemase types such as metalloenzymes and KPC have been commonly observed, while the OXA-48 type is rare. Only one relevant case report has been found so far, where a combination of multiple drugs, including Polymyxa B and cefideril, was used. Due to its side effects, including nephrotoxicity and neurological issues, as well as a lack of data on its administration in newborns/ infants, Polymyxa B may not be the best antibiotic choice. Some studies recommend combining CAZ-AVI with amikacin.[42] In the case of this child, initial treatment combined with amikacin yielded poor efficacy. Premature infants have incomplete nephrogenesis, inadequate plasma drug concentration of amikacin may be a crucial factor contributing to the treatment failure.[34–36] Previous reports have indicated that the combination of CAZ-AVI and ATM exhibits significant in vitro activity against CPE expressing multiple beta-lactamases.[31] A recent study conducted on CPE isolated from clinical samples also demonstrated a synergistic effect of the combination of CAZ-AVI and ATM on 98.8% of *Klebsiella* spp, with all 16 pan drug-resistant (PDR) isolates showing a synergistic effect.[32] In our study, the combined susceptibility test revealed a significant synergistic effect between CAZ-AVI, and ATM, but not with amikacin. It is important to note that although the *Klebsiella pneumoniae* strain in our case is resistant to ATM, avibactam (AVI) acts as a beta-lactamase inhibitor, protecting ATM from hydrolysis by various beta-lactamases, including ESBLs and *Klebsiella*

Table 3 Reports of CRKP Infections in Premature Infants

Publication	Age, Sex	Gestational Age (W), Weight at Birth (g)	Diagnosis	Culture	Notes	Susceptible Drug	Ineffective Antimicrobial Therapy	Definitive Antimicrobial Therapy	Outcome
Current case	After delivery, M	32, 1370	Premature infant, VLBW infant, and neonatal respiratory distress syndrome; neonatal sepsis and septic shock; NEC	Blood	OXA-48, ESBL	TGC, AMK, GEN and tobramycin; intermediate susceptibility to cefoperazone-sulbactam	MEM; cefoperazone-sulbactam + AMK; CAZ-AVI + AMK + Van	CAZ-AVI (62.5mg/kg q8h), ATM (30mg/kg q6h) and FOF (33mg/kg q8h), for 15 days.	Cured
Sameer Bawankule et al 2023[22]	Referred to our hospital at day 9, M	27, 1040	Complications of hyaline membrane disease, PDA, and suspected NEC	NR	MBL (NDM) and OXA-48-like	CST	CST + MEM; polymyxin B + CAZ-AVI + ATM	cefiderocol, polymyxin B, CAZ-AVI, and ATM, for 14 days.	Cured
Caterina Monari et al 2023[21]	After delivery, F	31+1, 1100	BSI	Blood	MBL (VIM)	Cefiderocol; intermediate susceptibility to IPM	SAM + netilmicin (intolerance); Van + netilmicin; MEM	Cefiderocol (60mg/kg loading dose, followed by 40mg/kg q8h), for 9 days.	Cured
Weicong Pu et al 2023[19]	7-hour-old, F	34+4, 2400	Osteoarthritis	Blood	CRKP	Polymyxin, CHL and TGC, after treatment with polymyxin for 4 weeks, indicated resistance to polymyxin	MEM; polymyxin	CAZ-AVI (50mg/kg q8h), for 2 weeks.	Cured
Weicong Pu et al 2023[19]	45-day-old, M	32+4, 1270	Right hip arthritis and femoral osteomyelitis	Puncture fluid	CRKP	TET, minocycline, TGC, compound TMP–SMZ, CHL, polymyxin and CAZ-AVI	MEM + Van	CAZ-AVI (50mg/kg q8h), for 4 weeks.	Cured
Andrea Marino et al 2023[17]	After delivery, M	25+3940	Klebsiella pneumoniae bacteremia	Blood	KPC	CST, TGC, FOF, TMP–SMZ, CAZ-AVI, ceftolozane-tazobactam	Specific drugs were not reported	CAZ-AVI (50mg/kg q8h) along with FOF or AMK (not report clear), for 15 days.	Cured
Allan da S. Nascimento et al 2022[20]	After delivery, NR	29, 830	BSI	Blood	CPKP, ESBL	AMK, CST, and CAZ-AVI	N	CAZ-AVI (50mg/kg q8h for 2 days; next two days adjusted to peritoneal dialysis to 23.75mg/kg q48h; followed by 50mg/kg q8h), totally for 2 weeks.	Cured
Suzan S. Asfour et al 2022[23]	After delivery, F	27, 920	Bacteraemia and meningitis	Blood and CSF	CRKP	Blood culture showed sensitive to CST, GEN, TGC. The CSF culture was sensitive to CST.	MEM + Van; CST + GEN	CAZ-AVI (62.5mg/kg q8h) and FOF, for 2 weeks.	Cured
Suzan S. Asfour et al 2022[23]	After delivery, F	28, 925	Bacteraemia	Blood	CRKP, ESBL	Initially, sensitive to MEM and AMK. After 15 days sensitive to CAZ-AVI and AMK	cefepime + AMK; MEM + AMK	CAZ-AVI (62.5mg/kg q8h for 4 days and 62.5mg/kg qd for 1 day) and AMK, totally for 5 days.	Died
Yesim Coskun et al 2020[26]	After delivery, NR	27, 1000	UTI	Urine	CRKP	TGC	MEM + AMK; MEM + CST	CAZ-AVI (50mg/kg q8h), for 10 days.	Cured

(*Continued*)

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Table 3 (Continued).

Publication	Age, Sex	Gestational Age (W), Weight at Birth (g)	Diagnosis	Culture	Notes	Susceptible Drug	Ineffective Antimicrobial Therapy	Definitive Antimicrobial Therapy	Outcome
Elias Iosifidis et al 2019[27]	Median age 51 days, range from 13 days to 134 days, 3M, 2F	25–32, median weight 1260g, range from 900g to 2030g	NEC, EOS, LOS and other diagnoses	Blood or rectal swab	CRKP	All patients were susceptible to CAZ-AVI, most (4/5) susceptibility to CST, 1 patient were intermediate susceptible to AMK	All patients received other antibiotics prior to CAZ-AVI.	Other antibiotics and CAZ-AVI (62.5mg/kg q8h. In one case of febrile UTI due to renal insufficiency and CVVH, the dose was given at 50% of the recommended dose q8h.)	Cured
Bowen Weng et al 2021[24]	At 1 hour postnatally, M	28+1, 970	Sepsis	TI, sputum, and blood	CRKP	CAZ-AVI, polymyxin B, TMP-SMZ and TGC	Van	TMP–SMZ (20mg/kg, bid), for 10 days.	Cured
Yue-E Wu et al 2020[25]	After delivery, NR	27, 972	Neonatal sepsis, neonatal meningitis	Blood	CRKP	Levofloxacin and AMK	N	MEM 20mg/kg q12h for 4 days, then 40mg/kg q12h for 3 days.	Cured
Matilde Ciccia et al 2018[28]	After delivery, F	25+1, 750	Severe VAP with concomitant bacteraemia	Blood and BAL	MBL (VIM)	TGC and CST	oxacillin + GEN; TZP + GEN	MEM (60mg/kg, qid), GEN and aerosolised GEN (0.6 mg in 2 mL of normal saline qid), for 10 days.	Cured
Paolo Bonfanti et al 2017[29]	After delivery, NR	23, 540	Sepsis	Blood and BA	KPC-3	GEN and CST	N	MEM (20mg/kg q8h) and CST (2.5mg/kg bid), for 10 day.	Cured
Javier Antonio Escobar Pérez et al 2013[30]	Median age 11.5 days, range from 9 days to 23 days, 2M, 2F	29–32, median weight 1375g, range from 1000g to 1660g	Placenta abruptio, severe perinatal asphyxia, enterocolitis, and other diagnoses.	Blood, catheter tip, feces and peritoneal fluid.	MBL (NDM-1)	ATM, CIP, TET, TGC, and CST	AMP + AMK; AMP + TZP; TZP+ GEN	MEM + rifampin; IPM + CIP	3 cured and 1 died
Debasmita Dubey et al 2013[31]	7-day-old, NR	31, 1250	Neonatal septicemia	Blood	MBL, ESBL	N (resistant to 17 antibiotics)	TZP + GEN	N	Died

Abbreviations: F, female; NR, not report; M, male; W, week; VLBW, very low birth weight; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; BSI, Bloodstream infection; UTI, urinary tract infection; EOS, early onset sepsis; LOS, late-onset sepsis; CSF, cerebrospinal fluid; TI, tracheal intubation; BAL, bronchoalveolar lavage; BA, bronchial aspirate; ESBL, extended-spectrum beta-lactamases; MBL, metallo-beta-lactamases; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CPKP, carbapenemase-producing *Klebsiella pneumoniae*; TGC, tigecycline; AMK, amikacin; GEN, gentamicin; CST, colistin; CAZ-AVI, ceftazidime-avibactam; TMP–SMZ, trimethoprim-sulfamethoxazole; IPM, imipenem; CHL, chloramphenicol; TET, tetracycline; FOF, fosfomycin; MEM, meropenem; ATM, aztreonam; CIP, ciprofloxacin; Van, vancomycin; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; AMP, ampicillin; CVVH, continuous venous-venous hemofiltration.

pneumoniae carbapenemase (KPC).[33] This mechanism may explain the observed synergistic effect of CAZ-AVI and ATM in vitro. Additionally, despite the use of the CAZ-AVI and ATM, this infant's condition remained unstable As an innovative approach, fosfomycin was added as the third combination drug in our case. Recent research indicates that fosfomycin's unique mechanism of action allows for synergistic effects with other antibacterial drugs in treating CRE without cross-resistance. However, there is limited pharmacokinetic data for fosfomycin in premature infants. Current literature suggests a recommended daily total dose of intravenous fosfomycin sodium for children and newborns with normal renal function in European countries is typically 200 to 400 mg/kg, administered 2 to 3 times daily. To account for the renal function status of premature infants, a daily dose of 100 mg/kg was administered, divided into 3 doses per day. Ultimately, this approach achieved a "powerful combination" for treating pathogens that produce both ESBL and OXA-48, throughout this treatment period, we closely monitored the infant's renal function and electrolyte levels, observing no adverse reactions.

Inadequate source control may have contributed to incomplete bacteremia clearance and the development of antibiotic-resistant strains. Upon evaluation, it was found that the Peripherally Inserted Central Catheter (PICC) had been in place for one month. Additionally, there were drainage tubes and an ostomy bag. After removing the PICC, cleaning and replacing the fistula tube, there was a significant improvement in the infection symptoms of the child. This emphasizes the importance of not only administering appropriate and effective antimicrobials but also considering necessary surgical intervention and providing appropriate care. This case also serves as a reminder that premature infants with low birth weight, who require mechanical ventilation for respiratory support, use broad-spectrum antibacterial drugs, long-term intravenous nutrition, and have a PICC indwelling are at high risk for hospital-acquired Carbapenem-Resistant Enterobacteriaceae (CRE) infection.

Our study describes the successful recovery of a premature infant infected with *Klebsiella pneumoniae* that produces extended-spectrum beta-lactamase (ESBL) and OXA-48 enzymes. The child's condition improved through a combination regimen of ceftazidime-avibactam (CAZ-AVI), aztreonam (ATM), and fosfomycin, along with successful surgery and optimized management of PICC. Our research findings highlight the importance of utilizing multiple methods to detect the cause of infection when initial treatment fails. Additionally, combined drug susceptibility testing can assist in determining appropriate dosing regimens for OXA-48-producing *Klebsiella pneumoniae*, with CAZ-AVI and ATM demonstrating a positive synergistic effect. Furthermore, fosfomycin proves to be a valuable option as a third drug in the combination regimen, particularly in severe infections, yielding good therapeutic outcomes. While existing literature suggests that CAZ-AVI is well tolerated in preterm infants, further prospective clinical trials are necessary to thoroughly evaluate its safety and efficacy in this specific population. In our case, the combination regimen was well tolerated, and no significant adverse drug reactions were observed.

Ethics Approval

The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Approval Number: 2023-E758-01). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed Consent

Written informed consent for publication of their details was obtained from the parents, and the publication of this paper will not disclose the patient's identity information, and there will be no interest disputes with the patient and his family.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors have no competing interests to declare that are relevant to the content of this article.

References

1. Podschun R, Ullmann U. Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. *Clin Microbiol Rev*. 1998;11(4):589–603. doi:10.1128/CMR.11.4.589
2. Sands K, Carvalho MJ, Portal E, et al. Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. *Nat Microbiol*. 2021;6(4):512–523. doi:10.1038/s41564-021-00870-7
3. Han YL, Wen XH, Zhao W, et al. Epidemiological characteristics and molecular evolution mechanisms of carbapenem-resistant hypervirulent Klebsiella pneumoniae. *Front Microbiol*. 2022;13:1003783. doi:10.3389/fmicb.2022.1003783
4. Pu D, Zhao J, Chang K, Zhuo X, Cao B. "Superbugs" with hypervirulence and carbapenem resistance in Klebsiella pneumoniae: the rise of such emerging nosocomial pathogens in China. *Sci Bull*. 2023;68(21):2658–2670. doi:10.1016/j.scib.2023.09.040
5. Lin XC, Li CL, Zhang SY, Yang XF, Jiang M. The global and regional prevalence of hospital-acquired carbapenem-resistant Klebsiella pneumoniae infection: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2024;11(2):ofad649. doi:10.1093/ofid/ofad649
6. Hu F, Pan Y, Li H, et al. Carbapenem-resistant Klebsiella pneumoniae capsular types, antibiotic resistance and virulence factors in China: a longitudinal, multi-centre study. *Nat Microbiol*. 2024;9(3):814–829. doi:10.1038/s41564-024-01612-1
7. Hu Y, Yang Y, Feng Y, et al. Prevalence and clonal diversity of carbapenem-resistant Klebsiella pneumoniae causing neonatal infections: a systematic review of 128 articles across 30 countries. *PLoS Med*. 2023;20(6):e1004233. doi:10.1371/journal.pmed.1004233
8. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet*. 2017;390(10104):1770–1780. doi:10.1016/S0140-6736(17)31002-4
9. Russell NJ, Stöhr W, Plakkal N, et al. Patterns of antibiotic use, pathogens, and prediction of mortality in hospitalized neonates and young infants with sepsis: a global neonatal sepsis observational cohort study (NeoOBS). *PLoS Med*. 2023;20(6):e1004179. doi:10.1371/journal.pmed.1004179
10. Fu P, Xu H, Jing C, et al. Bacterial epidemiology and antimicrobial resistance profiles in children reported by the ISPED program in China, 2016 to 2020. *Microbiol Spectr*. 2021;9(3):e0028321. doi:10.1128/Spectrum.00283-21
11. Chiotos K, Hayes M, Gerber JS, Tamma PD. Treatment of carbapenem-resistant Enterobacteriaceae infections in children. *J Pediatric Infect Dis Soc*. 2020;9(1):56–66. doi:10.1093/jpids/piz085
12. Karampatakis T, Tsergouli K, Behzadi P. Carbapenem-resistant Klebsiella pneumoniae: virulence factors, molecular epidemiology and latest updates in treatment options. *Antibiotics*. 2023;12(2):234. doi:10.3390/antibiotics12020234
13. Katip W, Rayanakorn A, Oberdorfer P, Taruangsri P, Nampuan T, Okonogi S. Comparative effectiveness and mortality of colistin monotherapy versus colistin-fosfomycin combination therapy for the treatment of carbapenem-resistant Enterobacteriaceae (CRE) infections: a propensity score analysis. *J Infect Public Health*. 2024;17(5):727–734. doi:10.1016/j.jiph.2024.03.010
14. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clin Infect Dis*. 2023;1:3.
15. Yin D, Wu S, Yang Y, et al. Results from the China Antimicrobial Surveillance Network (CHINET) in 2017 of the in vitro activities of ceftazidime-avibactam and ceftolozane-tazobactam against clinical isolates of Enterobacteriaceae and Pseudomonas aeruginosa. *Antimicrob Agents Chemother*. 2019;63(4). doi:10.1128/AAC.02431-18
16. de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. In vitro susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible Enterobacteriaceae isolates collected during the INFORM global surveillance study (2012 to 2014). *Antimicrob Agents Chemother*. 2016;60(5):3163–3169. doi:10.1128/AAC.03042-15
17. Marino A, Pulvirenti S, Campanella E, et al. Ceftazidime-Avibactam treatment for Klebsiella pneumoniae bacteremia in preterm infants in NICU: a clinical experience. *Antibiotics*. 2023;12(7):1169. doi:10.3390/antibiotics12071169
18. Shirley M. Ceftazidime-avibactam: a review in the treatment of serious gram-negative bacterial infections. *Drugs*. 2018;78(6):675–692. doi:10.1007/s40265-018-0902-x
19. Pu W, Fan L, Zhang Y, You D, Li M, Ma L. Carbapenem-resistant Klebsiella pneumoniae osteoarthritis in two preterm infants treated with ceftazidime-avibactam. *Pediatr Infect Dis J*. 2023;42(12):1124–1127. doi:10.1097/INF.0000000000004092
20. Nascimento ADS, Passaro MF, Silva PSS, et al. Off-label use of ceftazidime-avibactam in a premature infant with multidrug-resistant Klebsiella pneumoniae infection: a case report. *J Pharm Pract*. 2023;36(4):1020–1025. doi:10.1177/08971900221087131
21. Monari C, Spagnuolo F, Pisaturo M, et al. Bloodstream infection due to a VIM-metallo-β-lactamase-producing Klebsiella pneumoniae treated with cefiderocol in a preterm newborn. *Infect Dis Ther*. 2023;12(2):727–734. doi:10.1007/s40121-022-00735-4
22. Bawankule S, Nabar N, Joshi P, Singhal T. Cefiderocol as salvage therapy for carbapenem-resistant Klebsiella pneumoniae sepsis in an extremely preterm neonate. *Indian J Pediatr*. 2023;90(3):310. doi:10.1007/s12098-022-04468-7
23. Asfour SS, Alaklobi FA, Abdelrahim A, et al. Intravenous ceftazidime-avibactam in extremely premature neonates with carbapenem-resistant Enterobacteriaceae: two case reports. *J Pediatr Pharmacol Ther*. 2022;27(2):192–197. doi:10.5863/1551-6776-27.2.192
24. Weng B, Zhang X, Hong W, Yan C, Gong X, Cai C. A case of sepsis due to carbapenem-resistant Klebsiella pneumoniae in an extremely low-birth weight infant treated with trimethoprim-sulfamethoxazole. *Infect Drug Resist*. 2021;14:2321–2325. doi:10.2147/IDR.S312183
25. Wu YE, Xu HY, Shi HY, van den Anker J, Chen XY, Zhao W. Carbapenem-Resistant Enterobacteriaceae bloodstream infection treated successfully with high-dose meropenem in a preterm neonate. *Front Pharmacol*. 2020;11:566060. doi:10.3389/fphar.2020.566060

26. Coskun Y, Atici S. Successful treatment of pandrug-resistant Klebsiella pneumoniae infection with ceftazidime-avibactam in a preterm infant: a case report. *Pediatr Infect Dis J*. 2020;39(9):854–856. doi:10.1097/INF.0000000000002807
27. Iosifidis E, Chorafa E, Agakidou E, et al. Use of ceftazidime-avibactam for the treatment of extensively drug-resistant or pan drug-resistant Klebsiella pneumoniae in neonates and children <5 years of age. *Pediatr Infect Dis J*. 2019;38(8):812–815. doi:10.1097/INF.0000000000002344
28. Ciccia M, Ambretti S, Guerra L, Sandri F. Verona integron-encoded metallo-β-lactamase-producing Klebsiella pneumoniae sepsis in an extremely premature infant. *Case Rep Perin Med*. 2018;7(2). doi:10.1515/crpm-2018-0011
29. Bonfanti P, Bellù R, Principe L, et al. Mother-to-child transmission of KPC carbapenemase-producing Klebsiella pneumoniae at birth. *Pediatr Infect Dis J*. 2017;36(2):228–229. doi:10.1097/INF.0000000000001403
30. Escobar Pérez JA, Olarte Escobar NM, Castro-Cardozo B, et al. Outbreak of NDM-1-producing Klebsiella pneumoniae in a neonatal unit in Colombia. *Antimicrob Agents Chemother*. 2013;57(4):1957–1960. doi:10.1128/AAC.01447-12
31. Dubey D, Sarangi R, Debata NK, Padhy RN. Detection of metallo β-lactamase producing Klebsiella pneumoniae in a neonatal septicemia. *J Acute Dis*. 2013;2(1):82–84. doi:10.1016/S2221-6189(13)60104-3
32. Leiyan H, Pan F, Xia W, et al. Antimicrobial resistance profile of clinical strains isolated from children in China: a report from the ISPED program of 2020 (in Chinese). *Chin J Evid Based Pediatr*. 2021;16(06):414–420.
33. Pan F, Chuanqing W, Hui Y, et al. Antimicrobial resistance profile of clinical strains isolated from children in China: a report from the ISPED program in 2021 (in Chinese). *Chin J Evid Based Pediatr*. 2022;17(05):355–362.
34. Pan F, Chuanqing W, Hui Y, et al. Antimicrobial resistance profile of clinical strains isolated from children in China: report from the ISPED program in 2022 (in Chinese). *Chin J Evid Based Pediatr*. 2023;18(05):341–348.
35. Fu P, Luo X, Shen J, et al. The molecular and epidemiological characteristics of carbapenemase-producing Enterobacteriaceae isolated from children in Shanghai, China, 2016–2021. *J Microbiol Immunol Infect*. 2023;56(1):48–56. doi:10.1016/j.jmii.2022.07.012
36. Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: the phantom menace. *J Antimicrob Chemother*. 2012;67(7):1597–1606. doi:10.1093/jac/dks121
37. Aracil-Gisbert S, Fernández-De-Bobadilla MD, Guerra-Pinto N, et al. The ICU environment contributes to the endemicity of the "Serratia marcescens complex" in the hospital setting. *mBio*. 2024;15(5):e0305423. doi:10.1128/mbio.03054-23
38. Bonomo RA, Burd EM, Conly J, et al. Carbapenemase-Producing Organisms: a Global Scourge. *Clin Infect Dis*. 2018;66(8):1290–1297. doi:10.1093/cid/cix893
39. Potron A, Poirel L, Nordmann P. Derepressed transfer properties leading to the efficient spread of the plasmid encoding carbapenemase OXA-48. *Antimicrob Agents Chemother*. 2014;58(1):467–471. doi:10.1128/AAC.01344-13
40. Aghamohammad S, Khazani Asforooshani M, Malek Mohammadi Y, Sholeh M, Badmasti F. Decoding the genetic structure of conjugative plasmids in international clones of Klebsiella pneumoniae: a deep dive into blaKPC, blaNDM, blaOXA-48, and blaGES genes. *PLoS One*. 2023;18(11):e0292288. doi:10.1371/journal.pone.0292288
41. Stewart A, Harris P, Henderson A, Paterson D. Treatment of Infections by OXA-48-Producing Enterobacteriaceae. *Antimicrob Agents Chemother*. 2018;62(11). doi:10.1128/AAC.01195-18
42. Lin LY, Debabov D, Chang W, Stone G, Riccobene T. Antimicrobial activity of ceftazidime-avibactam and comparators against pathogens harboring OXA-48 and AmpC Alone or in Combination with Other β-Lactamases Collected from Phase 3 Clinical Trials and an International Surveillance Program. *Antimicrob Agents Chemother*. 2022;66(3):e0198521. doi:10.1128/aac.01985-21
43. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis*. 2017;17(7):726–734. doi:10.1016/S1473-3099(17)30228-1
44. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al. A predictive model of mortality in patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae. *Mayo Clin Proc*. 2016;91(10):1362–1371. doi:10.1016/j.mayocp.2016.06.024