

Ceftazidime-Avibactam/Aztreonam Combination for the Treatment of Carbapenem-resistant *Klebsiella pneumoniae*-induced Osteomyelitis: A Case Series with Review of Literature

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Learning Point of the Article:

Ceftazidime-Avibactam/Aztreonam combination has been shown to be useful in management of carbapenem-resistant *Klebsiella pneumoniae*-induced bone and soft-tissue infections.

Abstract

Introduction: Osteomyelitis secondary to multi-drug resistant (MDR) gram-negative bacteria (GNB), especially Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), is a rare occurrence. These are difficult to treat micro-organisms and their presence within the host bone tissue makes them inherently resistant to most standard antimicrobials. Although a number of drugs have been described in the literature, there are no standardized guidelines as to the ideal drug of choice effective against CRKP-induced bone and joint infections (BJIs). In this context, we have described our experience in treating three cases of CRKP osteomyelitis secondary to an open fracture, who presented to us following a road-traffic accident (RTA).

Case Report: Three patients of polytrauma presented to the emergency room of a tertiary care institute following RTA. All of them were primarily resuscitated, following which fixation of the fractures was undertaken. In the post-operative period, surgical site infection was seen in all three at specific locations. These were thoroughly debrided, and intraoperative samples sent for culture analyses. The latter revealed isolates of CRKP. Accordingly, a multidisciplinary approach was followed, combining inputs from the surgical team, clinical microbiologist, as well as an infectious disease specialist. Infected implants were removed, and a plastic surgery consult sought for wound coverage. Ceftazidime-Avibactam (CAZ-AVI) in conjunction with Aztreonam (ATM) was started after synergy testing. This was continued for a duration of 4–6 weeks. In two patients, the fracture had successfully united, whereas in one, a definitive fixation is still pending. Soft-tissue envelope healing was achieved in all cases. No adverse effects were reported.

Conclusion: Cases of BJI secondary to CRKP necessitate a combined approach which includes prompt surgical debridement with/without implant removal and culture-specific antimicrobial therapy. Although experience is limited, CAZ-AVI/ATM combination has shown promising results.

Keywords: Carbapenem-resistant *Klebsiella pneumoniae*, multi-drug-resistant Gram-negative bacteria, osteomyelitis, ceftazidime-avibactam/aztreonam.

Author's Photo Gallery



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Introduction

Bone and joint infections (BJI) are one of the most challenging problems faced by orthopedic surgeons. The key to successful management is a multidisciplinary approach with timely diagnosis, appropriate surgical treatment, and microbe-specific antibiotic therapy. While *Staphylococcus aureus* is the most commonly implicated micro-organism in osteomyelitis, the incidence of multidrug-resistant (MDR) Enterobacteriaceae, particularly Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), is on the rise [1,2]. Although rare, these represent a major public health problem and are associated with significant morbidity and mortality [3,4].

A number of antibiotic therapies have been described for the management of CRKP-induced BJIs [5,6,7]. Out of these, β -lactamase inhibitor combinations such as Ceftazidime-Avibactam (CAZ-AVI) or Aztreonam-Avibactam (ATM-AVI) constitute a newer class of antibiotics that have shown promising results in in-vitro models [6,8,9]. While individual reports/case series exist documenting the efficacy of CAZ-AVI alone or in combination with ATM in treating CRKP-induced osteomyelitis, there are no large-scale prospective studies for

the same [10,11,12,13,14,15]. ATM-AVI, on the other hand, is yet to be approved by the United States Food and Drug Administration (U.S. FDA) for use in BJIs [5,13].

Due to a lack of standardized treatment guidelines, we have described our own experience in successfully managing three cases of BJI secondary to CRKP in a tertiary care center of Western India.

Case Report

Case 1

A forty-seven-year-old male presented to the Emergency room (ER) with an alleged history of road traffic accident (RTA) 2 days back. The patient was diagnosed with an open grade IIIB fracture of the distal 1/3rd right femur with an associated fracture in the ipsilateral shaft of the tibia (Fig. 1a, b, c). There was accompanying internal degloving of the skin and subcutaneous tissue over the anteromedial aspect of the right thigh (Fig. 1d). The patient was taken up for emergency surgery and underwent debridement of the degloved area along with open reduction internal fixation (ORIF) (for femur) as well as

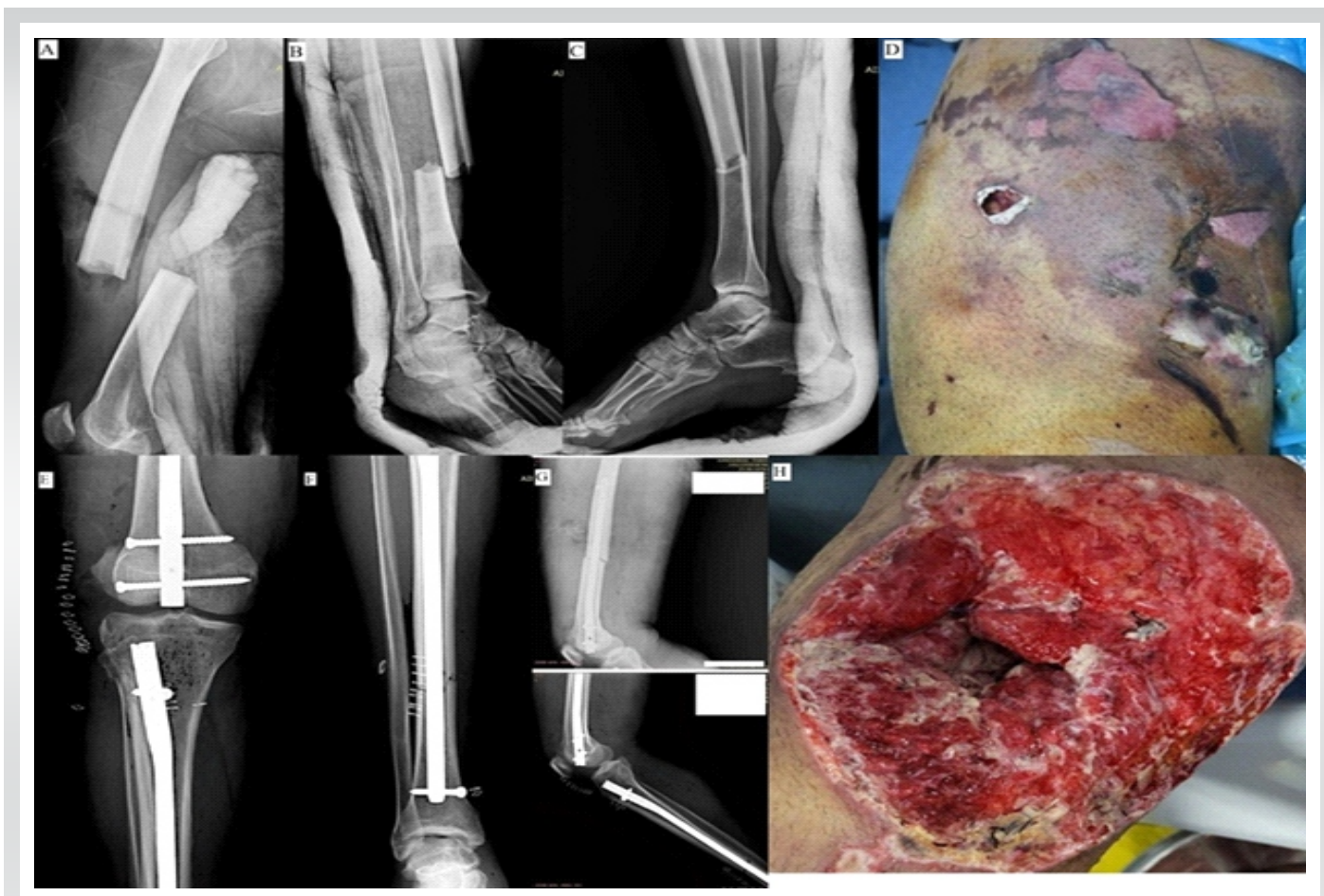


Figure 1: (a, b, c) Pre-operative X-rays; (d) Clinical representation of the injured thigh at the time of presentation; (e, f, g) Immediate post-operative X-rays; (h) Thigh wound following debridement (post-operative day 5).

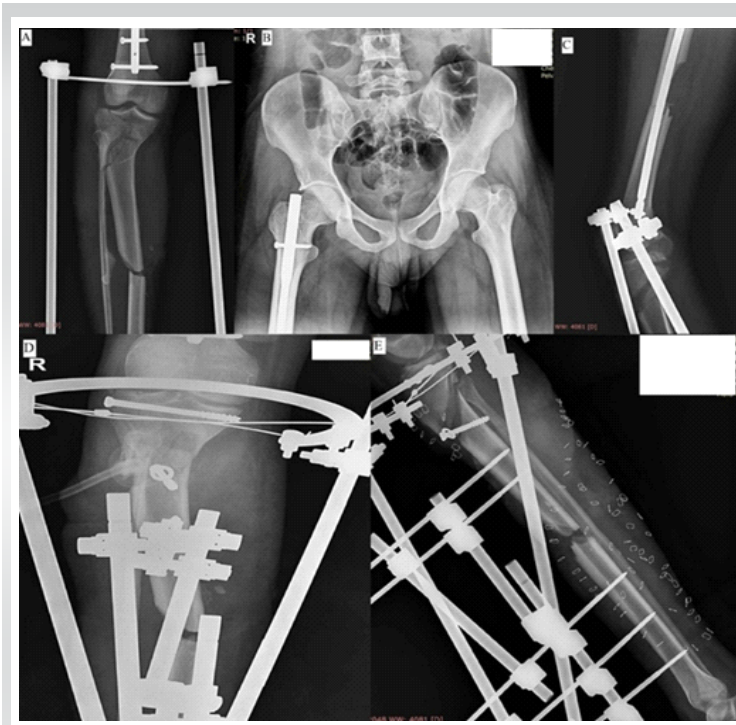


Figure 2: (a, b, c) X-rays of the patient at the time of hospital admission; (d and e) Immediate post-operative X-rays.

closed reduction internal fixation (for tibia) (Fig. 1e, f, g). On the 4th post-operative day, purulent discharge was noted from the raw area over the thigh. This was accompanied by intermittent febrile episodes (temperature $>101^{\circ}\text{F}$), elevated total leucocyte counts (TLC = $16010/\mu\text{L}$) and raised serum erythrocyte sedimentation rates (ESR = 105 mm/h) as well as highly sensitive C-reactive protein (hs-CRP = 202 mg/L). Patient was taken up for re-debridement and freshening of the skin margins (Fig. 1h). However, in the immediate post-operative period, his condition further deteriorated with TLC, ESR, and hs-CRP spiking to $21000/\mu\text{L}$, 134 mm/h , and 287.7 mg/L . Ultrasonography (USG) showed a small echogenic collection in the right knee. As a result, the patient underwent surgical exploration and evacuation of the collection. Intraoperatively tissue samples were found to be positive for CRKP. Antibiotic sensitivity

testing was done using the VITEK[®]2 automated analyzer (BioMérieux, France) and revealed sensitivity only to Colistin (Intermediate sensitivity MIC $<0.5\text{ mcg/mL}$) and Tigecycline (Sensitive MIC $<0.5\text{ mcg/mL}$). Synergy testing showed affirmative results with CAZ-AVI and ATM combination. The patient was started on intravenous antibiotics-CAZ-AVI and ATM at the dosage of 2.5 g q8h and 2 gq8h for a total of 4 weeks. Raw area over the thigh was covered with a free anterolateral thigh flap. At 12 months follow-up, the patient has a healthy wound and can ambulate freely.

Case 2

A twenty-nine-year-old male patient suffered RTA and was diagnosed with an open Grade IIIA fracture right mid-shaft femur, along with an open Grade IIIB fracture of the right proximal tibial shaft (segmental). He was initially operated at the primary hospital of presentation and underwent ORIF using an interlocking nail for the femur and external fixation for the tibia (Fig. 2a, b, c). However, from post-operative day 2, an active wound discharge was noted over the anterior aspect of the leg. Lab parameters showed the following values: TLC – $18250/\mu\text{L}$; ESR – 100 mm/h , and hs-CRP- 233.9 mg/L . Patient was subsequently referred to our institute, where he underwent debridement of the tibial wound as well as fixator re-application. An additional injury was detected over the right tibial plateau, which was fixed using two 6.0 mm cannulated cancellous screws (Fig. 2d and e). Intraoperative tissue samples were cultured and found to be positive for MDR



Figure 3: (a, b, c, d) Intraoperative images of the tibial defect showing exposed bone and the (e, f, g) final wound status at 9 months follow-up.



Figure 4: (a, b, c, d, e) Pre-operative radiographs showing fractures of the distal femur, elbow, ankle, and the foot; (f) High wound at presentation; (g and h) Lacerations and degloving injuries of the foot area.

K. pneumoniae. The latter showed sensitivity to only Tigecycline (MIC = 1 mcg/mL), Colistin (MIC < 0.5 mcg/mL) (Intermediate sensitive), as well as CAZ-AVI/ATM combination (positive synergy testing using the disc diffusion method). The case was discussed with an infectious disease specialist, and accordingly, the patient was started on intravenous CAZ-AVI 2.5g q8h + ATM 2g q8h for a total of 6 weeks. Plastic surgery review was done for the tibial wound defect (Fig. 3a, b, c, d, e, f, g). This involved coverage with a lateral gastromyocutaneous flap for the middle third and a medial gastrocnemius flap + split skin grafting for the upper third leg wound with implant (Fig. 3a, b, c, d, e, f, g). After 6 weeks, the patient underwent fixator removal, and antibiotics were stopped. At 12 months follow-up patient is afebrile, has a completely healed soft-tissue coverage, and is planned for a definite tibial fixation.

Case 3

A thirty-five-year-old victim of polytrauma presented to the ER following RTA. He was diagnosed with several bony injuries to the upper and lower limbs (Fig. 4a, b, c, d, e, f, g, h). After initial resuscitation, all open fractures were copiously irrigated and splinted. Broad-

spectrum antibiotic and tetanus prophylaxis were given. After stabilization in the ER, the patient underwent staged fixation of the bony injuries. This involved the application of a knee-spanning external fixator frame to support the distal femur. The latter was switched to a locking plate after 3 weeks (Fig. 5a, b, c, d, e, f, g, h). On post-operative day 2 following ORIF, the patient developed fever spikes (temperature > 100°F) with TLC, ESR, and hs-CRP documented at 13,800/ μ L, 105 mm/h, as well as 294 mg/L, respectively. USG revealed an echogenic collection at the operative site. As a result, debridement and lavage of the surgical site were carried out, followed by plate removal and fixator re-application (Fig. 5i). Samples sent intra-operatively for microbiological analyses revealed growth of MDR K. pneumoniae by the VITEK®2 automated analyzer

(BioMérieux, France). Intermediate and complete sensitivity was noted to Colistin (MIC < 0.5 mcg/mL) and Tigecycline (MIC < 0.5 mcg/mL) while CAZ-AVI and ATM showed positive synergy. After discussion with an infectious disease specialist, the patient was started on a 4-week course of IV CAZ-AVI (2.5 g q8h) + ATM (2 g q8h). Raw areas over the foot and thigh were treated with regular dressings as per the plastic surgeon's advice. After 1 month, the patient's infection had settled and the raw areas healed (Fig. 5j, k, l). TLC had returned to normal limits (6000/ μ L) and inflammatory markers to their baseline values (ESR - 34 mm/h and hs-CRP - 14 mg/L). The patient was planned for definite distal femur fixation. However, he refused to undergo an additional surgical procedure, and



Figure 5: (a, b, c, d, e, f, g, h, i) Radiographs showing sequence of fixation of all bony injuries; (j, i, k, l) clinical images showing progressive healing of the infected thigh wound.

Table 1: A summary of all cases of Carbapenem-resistant *Klebsiella pneumoniae* -induced bone/joint infections and their management strategies

S. No.	Author/year	No. of cases	Average age (years)	Sites involved	Implant removal (Yes/No/NA)	Antibiotic therapy	Mean follow-up (months)
1	Barbosa <i>et al.</i> , 2025 [15]	1	46	OM:	NA	CAZ-AVI 2000/500 mg IV q8h for 6 weeks	12
				• Right midfoot,			
				• Multiple tarsal bones and • Epiphyses of leg			
2	Cani <i>et al.</i> , 2017 [10]	1	60	Vertebral OM:	No	CAZ-AVI 2.5g IV q8h (6 weeks)+short course Amikacin (13 days)	3
				• S1 vertebra+sacroiliac joint • Associated infected implants			
3	Mittal <i>et al.</i> , 2018 [14]	1	42	Extensive upper extremity OM:	External fixator was applied	CAZ-AVI 2.5g IV q8h+ATM 2g IV q8h (6 weeks) Adjunct antifungal: Liposomal amphotericin B→Polymyxin B; posaconazole (oral) (6 months)	NM
				• Right forearm degloving injury			
				• Open elbow fractures			
4	He <i>et al.</i> , 2025 [20]	1	28	SA left knee	NA	(Meropenem 1g IV q8h×3 days)+(Tigecycline 100 mg IV q12h×2 days) Switched to CAZ- AVI 2.5g IV q8h×6 days Switched back to Tigecycline 100 mg IV q12h×2 days after granulocyte counts normal For SA: CAZ-AVI 2.5g IV q8h×9 days	NM
5	Ji <i>et al.</i> , 2021 [13]	1	1.5 months old infant	SA right shoulder	NA	IPM-CLN started at 60 mg q6h Fosfomycin 440 mg q8h added for 3 days CAZ-AVI 200 mg IV q8h×14 days f/b Meropenem 200 mg IV q8h	0.5
6	Odio <i>et al.</i> , 2015 [7]	4	(1) 68	(1) Sacral OM	NA	(1) Imipenem+ciprofloxacin	(1) Patient died
			(2) 75	(2) Sacral OM		(2) Tigecycline+colistimethate+amikacin	(2) Patient died
			(3) 70	(3) Metatarsal OM		(3) Tigecycline	(3) 1.1
			(4) 67	(4) TMA OM		(4) Tigecycline+colistimethate	(4) 1.7
7	Schimmentiet <i>et al.</i> , 2018 [12]	1	26	OM right distal femur	Yes	Started on Colistin (loading dose 9 million IU f/b 4.5 million IU BD)+Fosfomycin 4g IV q8h+Tigecycline (loading 100 mg f/b 50 mg BD) Switched to CAZ-AVI 2.5g IV q8h×2 weeks	7.5
8	Soriano <i>et al.</i> , 2023 [25]	7	NM	OM	NA	Ceftazidime-avibactam most often 2.0g/0.5g IV q8h (median 9 days)	NM
9	De León-Borrás <i>et al.</i> , 2018 [11]	1	36	Vertebral (L1-L2 diskitis/OM) with associated pre-vertebral abscess and bilateral psoas pyomyositis.	NA	Ceftazidime/Avibactam (CAZ/AVI) 2.5g IV q8h×6 weeks. Previously unsuccessful therapy with: Polymyxin B, Carbapenems and Amikacin for 6 weeks	NM
10	Present study 2025	3	(1) 47	(1) OM right distal femur+right knee SA	(1) No	CAZ-AVI (2.5g q8h)+ATM (2g q8h)×4-6 weeks	(1) 4
			(2) 29	(2) OM right proximal tibia	(2) No		(2) 3
			(3) 35	(3) OM right distal femur	(3) Yes		(3) 6

NA: Not applicable, NM: Not mentioned, OM: Osteomyelitis, SA: Septic arthritis, CAZ-AVI: Ceftazidime-Avibactam, ATM: Aztreonam, IPM-CLN: Imipenem-cilastatin, TMA: Trans metatarsal amputation site

hence, the injury was managed conservatively with a thigh splint. At 12 months follow-up, all fractures had united, and the patient is able to ambulate without support.

Discussion

The frequency of Gram-negative bacteria (GNB) induced osteomyelitis and prosthetic joint infections (PJIs) is

approximately 10% [9,16]. Out of these, the most commonly implicated micro-organisms are *Acinetobacter baumannii*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Enterobacter* spp. etc. Antimicrobial resistance in these microbes is broadly categorized into three types – (i) MDR if not susceptible to at least one agent in >3 antimicrobial classes; (ii) Extensively drug resistant if non-susceptible to at

least one agent in all but <2 antimicrobial categories, and (iii) Pan-drug resistant if not susceptible to any antimicrobial agent across all categories [17]. Although Carbapenems constitute high-end antibiotics, their resistance in intensive care units in the Indian subcontinent has reached an alarming 12–83% [5]. These β -lactamases include the Ambler class A (KPC enzymes), class B (Metallo Carbapenemase enzymes/MBLs such as NDM, IMP), class C (AmpC β -lactamases), as well as class D (Oxacillinases enzymes like OXA-48) enzymes [5, 6, 9]. Mortality in CRKP-induced infections can range from 22 to 70%, with higher rates reported in patients with associated comorbidities [6,18]. Timely detection of these agents, hence, is crucial to initiating microbe-specific antibiotic therapy and ensuring clinical cure.

BJIs are notorious for their complexity and pose significant treatment challenges. The main reasons for the same are – (i) Biofilm formation and (ii) Poor rates of antibiotic diffusion into host tissue [6,9]. In vitro models suggest that the low concentration of oxygen and nutrients in the biofilm environment is probably responsible for the phenotypic changes within the bacteria, leading to antibacterial tolerance [19]. Different categories of antibiotics are, therefore, recommended to be used in combination for combating CRE infections. These mainly include – Carbapenems, Meropenem-Vaborbactam (MER-VAB), Imipenem-Cilastatin-Relebactam (IMI-REL), Ceftolozane-Tazobactam, CAZ-AVI, Cefiderocol, Fosfomycin, Tigecycline, and Colistin [6,20,21]. Carbapenems have the broadest spectrum antimicrobial activity and possess a favorable pharmacokinetic profile vis-à-vis bone infections. However, they are ineffective against Carbapenemase-producing *K. pneumoniae*, even when combined with Colistin [6]. MER-VAB and IMI-REL are newly introduced carbapenem- β -lactamase inhibitor combination drugs, which have been found to be effective against CRKPs (IMI-REL shows good response against *P. aeruginosa* also). However, they fail to combat MBLs as well as the OXA-48 category of enzymes. They are also ineffective against *A. baumannii* strains primarily resistant to MER and IMI [22]. Ceftolozane-Tazobactam is a fifth-generation cephalosporin combination with a β -lactamase inhibitor, which has shown promising results against extended-spectrum β -lactamase enzymes and some MDR strains of *P. aeruginosa*. Combined with Colistin, the drug has demonstrated good anti-biofilm activity in in-vitro models and can be used in meropenem-resistant cases [22]. CAZ-AVI was introduced in 2015 and is FDA approved for intra-abdominal infections, urinary tract infections, hospital-acquired pneumoniae, as well as BJIs. It is currently the only β -lactamase inhibitor combination having good activity against the OXA-48 category of enzymes

[5,9,10,11,12,13,14,15,18,23]. The chief drawback is the limited effectiveness against MBLs such as NDM, which are quite prevalent in our part of the world. To offset this, ATM is usually added to CAZ-AVI as the former has good activity against both OXA-48 as well as NDMs. A new combination - ATM-AVI- is currently under clinical trials [24,25]. Cefiderocol is a siderophore cephalosporin approved in 2019, which has shown broad coverage against most GNB, such as *A. baumannii*, *Klebsiella* spp., and *P. aeruginosa*, including activity against all four Ambler class β -lactamases. It has been cleared for use under limited treatment options [26].

There are no clear-cut guidelines on the choice, combination, as well as duration of antibiotic therapy for CRKP-induced BJIs. This is due to a lack of comparative randomized trials or large-scale cohort studies. However, newer β lactam/ β lactamase inhibitor class of drugs has shown promising results both in patients as well as in vitro models [5,6,9,10,24]. In our series, all patients first underwent a radical debridement of the infected tissues, with/without implant removal, following which broad-spectrum antibiotics were initiated. Once the culture report was affirmative for CRKP, the case was discussed in the infectious disease conference of the institute, and patients started on combination therapy. In all cases, the infection was successfully treated, and patients made a full recovery. We believe CAZ-AVI with ATM constitutes a reliable choice of antimicrobial when confronted with MDR GNB such as *K. pneumoniae*. Future trends call for blinded trials on the same to give more robust evidence. A summary of CRKPs reported thus far and how they compare with our study is given in Table 1.

Conclusion

CRKPs represent a rare subset of MDR GNB, which are increasingly being implicated in BJIs. These require prompt surgical intervention, along with combination antimicrobial therapy. Although results may vary from case to case and the literature is still sparse, CAZ-AVI/ATM for a duration of 4–6 weeks has shown promising results.

Clinical Message

A multidisciplinary approach is warranted in all cases of MDR pyogenic osteomyelitis. Thorough surgical debridement, judicious fracture stabilization, and combination culture-sensitive antibiotic therapy are the mainstays to ensure optimal response. For cases afflicted with CRKPs, CAZ-AVI/ATM combination has been shown to be reliable.



Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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