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Case Reports

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Clinical Outcomes of Ceftazidime-Avibactam Against Carbapenem-Resistant Enterobacteriaceae in Descending Necrotising Mediastinitis: Case Report and Literature Review

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ABSTRACT

Background: Current antibiotic options for carbapenem-resistant Enterobacteriaceae (CRE) are limited. However, anagement of patients with descending necrotizing mediastinitis (DNM) colonized with CRE is urgently required, as it is associated with significant post-operative morbidity and mortality. Ceftazidime-avibactam represents a novel combination therapy for CRE.

Case Presentation: A 50-year-old male patient with clinical DNM and prolonged intensice care. The patient underwent repeated surgeries and experienced infections with K. Pneumoniae, Acinetobacter Sp., and Pseudomonas Sp. resistant to carbapenems. The patient was administered ceftazidime-avibactam for 6 days. However, the patient was declared death after 30-days.

Discussion: The administration of ceftazidime-avibactam yielded good clinical outcomes in CRE infections. Combination therapy had a higher survival rate compared to monotherapy and lower rates of resistance.

Conclusion: Ceftazidime-avibactam demonstrates effective and safe potential for the management of CRE infections.

Keywords: Descending Necrotizing Mediastinitis, Carbapenem-resistant Enterobacteriaceae, Ceftazidime-avibactam, Antibiotic Resistance, Case Report

List Abbreviation

CI	:	Confidence Interval
CRE	:	Carbapenem-resistant Enterobacteriaceae
CRP	:	C-reactive protein
CrCl	:	Creatinine Clearance
cIAI	:	Complicated intra-abdominal infections
cUTI	:	Complicated urinary tract infections
CZA	:	Ceftazidime-avibactam
DIC	:	Disseminated intravascular coagulation
DNM	:	Descending Necrotising Mediastinitis
DSWI	:	Deep sternal wound infections
FDA	:	Food and Drug Administration
ICU	:	Intensive Care Unit
MDR	:	Multidrug-resistant
OR	:	Odds Ratio
RSCM	:	Cipto Mangunkusumo General Hospital
VAS	:	Visual Analogue Scale
WBC	:	White Blood Cell (disebut juga sebagai leukositosis)

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Background

Descending necrotizing mediastinitis (DNM) is a severe infection of the mediastinal connective tissue, interpleural space, and surrounding chest organs [1]. Though rare, it has a high mortality rate of up to 40% despite optimal treatment [2]. DNM often arises as a complication of post-cardiac surgery sternotomy (incidence 1–2.65%), but also result from esophageal perforation or odontogenic abscesses [1,2]. Early mortality is usually due to airway obstruction or sepsis, while later stages are dominated by sepsis and antibiotic resistance [3]. Patients are commonly admitted to the ICU due to frequent nosocomial infections and varied antibiotic use [4].

Antibiotic resistance remains a major global health threat, contributing to an estimated 1.27 million deaths in 2019 [5]. In deep sternal wound infections (DSWI), common pathogens include *Staphylococcus spp*. and Gram-negative bacteria [6]. *Acinetobacter baumannii*, prevalent in post-cardiac surgery patients, is linked to high mortality (17–63%) from conditions like pneumonia, septic shock, and disseminated intravascular coagulation (DIC) [7]. These strains are often resistant to β-lactams and classified as multidrug-resistant (MDR). At Cipto Mangunkusumo General Hospital (RSCM), ICU and emergency isolates from Jan-Mar 2023 were dominated by *Klebsiella pneumoniae* (31%), *Acinetobacter spp.* (22%), and Enterobacter spp. (9%).Ceftazidime-avibactam (CZA), a combination of third-generation cephalosporin and a novel β-lactamase inhibitor, and is effective against MDR *Pseudomonas aeruginosa* and carbapenem-resistant *Enterobacteriaceae* (CRE), which include *Klebsiella spp., Enterobacter spp., E. coli, Citrobacter spp., and Serratia spp*. However, CZA lacks activity against carbapenem-resistant *A. baumannii* and metallo-β-lactamase-producing bacteria [8]. Currently, only few studies addressed the DNM management in CRE infections due to limited cases. Although CZA has shown promise in treating CRE-related complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), its role in DNM remains unclear. This case report aims to highlight the potential of CZA in treating DNM with CRE infection.

Cases Presentation

A 50-year-old male presented with a 3-hour history of bloody pus discharge from the neck, accompanied by severe pain (VAS 7) and progressive facial and neck swelling. Initial treatment at another facility with anti-inflammatories and acyclovir showed no improvement. He had no history of dental issues, diabetes, or hypertension. Examination revealed hyperemia and tenderness in the bilateral submandibular region extending to the upper thorax, a dry neck wound with pus and blood, and palpable crepitus from the neck to the substernal area. Labs showed leukocytosis (25,700/uL), elevated CRP (263 mg/dL), procalcitonin (141.2 ng/mL), and hypoalbuminemia (2.3 g/L), with normal renal function. X-ray imaging showed subcutaneous emphysema in the neck (Figure 1).

He underwent emergency cricothyroidotomy and debridement, then was admitted to ICU. Tissue culture revealed *Streptococcus constellatus* (sensitive to ampicillin, ampicillin, erythromycin, tetracycline, clindamycin, and cefotaxime). He received meropenem (3×1 g) and topical honey therapy. On day 10, the patient desaturated and developed supraventricular tachycardia; X-ray imaging suggested bilateral empyema. Therefore, sternotomy, decortication, debridement, and bilateral chest tube placement were performed (Figure 2).

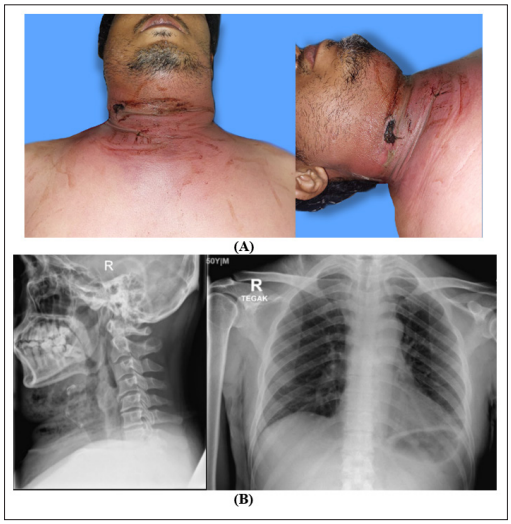

Figure 1: (A) Clinical photograph of the patient showing hyperemia from the submandibular region to the sternum accompanied by pus and blood discharge; (B) AP/lateral cervical X-ray; (C) AP chest X-ray

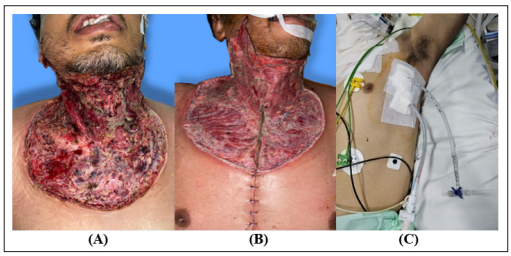

Figure 2: (A) Post cervicotomy and debridement; (B) sternotomy, dekortikasi, debridement, and chest tube insertion; (C) clinical photo of the drainage and chest tube

Second culture from bronchoalveolar lavage revealed *Acinetobacter sp., Klebsiella pneumoniae, and Pseudomonas fluorescens*. All pathogens showed carbapenem-resistant. No bacteraemia was found. Tigecycline and meropenem were administered, along with pleural irrigation and continued honey therapy. Despite this, infection markers worsened, prompting chest reopening and delayed sternal closure on day 20 (Figure 3). Other cultures showed resistant *Acinetobacter* and *Klebsiella*. Antibiotics were switched to CZA (3×2.5 g IV) and metronidazole (3×500 mg) for six days. However, the patient's condition deteriorated with worsening labs (WBC 50,830/uL, procalcitonin 16.56, CRP 121.7, CrCl 26.3 L/min), and pronounced deceased on day 30.

Discussion

A retrospective study by Balandin et al. showed that CZA was effective and safe for severe CRE infections, with 73.5% of patients improving and 68.0% discharged [9]. Shaw et al. reported a 60% recovery rate in carbapenem-resistant K. pneumoniae infections treated with CZA and aztreonam, with a 30-day mortality rate of 30% and a 33.3% recurrence rate at 90 days [10]. In a multicenter cohort, Tumbarello et al. found combination therapy (e.g., with fosfomycin, tigecycline, gentamicin, or meropenem) was more effective (70%) than CZA

monotherapy [11]. Notably, early CZA administration within 48 hours showed a 53.6% survival rate versus 16.3% for delayed or empirical therapy, though not statistically significant [11].

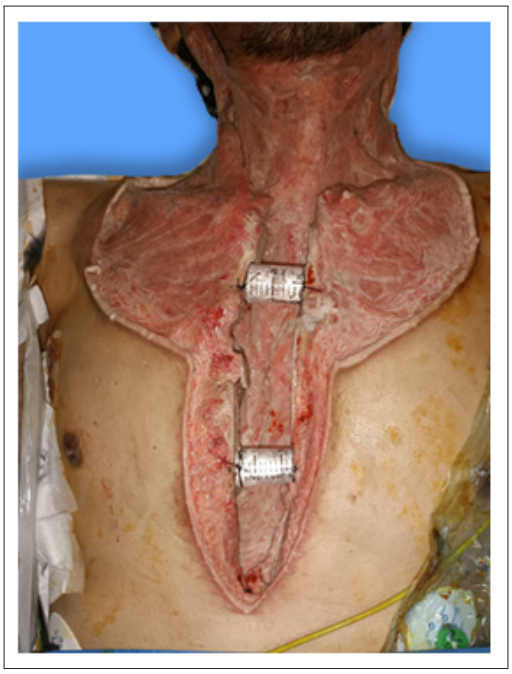

Figure 3: Chest reopening and delayed sternal closure on the 20th day of care

In this case, CZA plus metronidazole was started after 20 days of prior tigecycline and meropenem therapy. Sharma et al. reported 90.9% improvement by day 7-10 with CZA, comparable to 91.2% with standard regimens [12]. Ackley et al. found no significant difference in outcomes between CZA-based combinations (with meropenem or vaborbactam) and other regimens, but resistance developed with CZA monotherapy, supporting combination use [13]. In cIAI cases, CZA–metronidazole showed a 91.2% cure rate after two weeks, similar to meropenem (93.4%) [10]. However, a meta-analysis (503 patients) showed no mortality difference between CZA monotherapy and combination therapy (OR 0.96, 95% CI 0.65–1.41) [9]. Moreover, a Phase III FDA trial noted higher mortality with CZA (25.8%) vs. meropenem (8.6%) in patients with CrCl 30–50 mL/min [12]. Adverse effects of CZA include GI symptoms, anaphylaxis, skin reactions, seizures (especially in renal impairment), and QT prolongation [9,12]. Resistance to CZA, mainly due to β-lactamase mutations, is more common in P. aeruginosa (2.8–18%) than in Enterobacteriaceae [14].

Currently, no studies specifically assessed CZA for DNM. However, a case of CRE (K. pneumoniae) endocarditis post-mitral valve surgery showed successful recovery without bacteremia [15]. Another case post-neurosurgery with resistant P. aeruginosa responded to CZA–aztreonam after 60–100 days [16].

This study has limitations, including its retrospective, observational nature and lack of a control group, introducing potential bias. Treatment choice between monotherapy and combination was based on clinical judgment, and diverse infection types further limited analysis.

Conclusion

This study shows that CZA has effective and safe potential for the treatment of CRE infections. The clinical outcomes of CZA are better when administered after 48 hours of onset compared to empirical therapy. Combination therapy with Ceftazidime-avibactam and other antibiotics remains controversial, but the combination with Aztreonam shows promising results and warrants further investigation. It is important to note that monotherapy with CZA carries a higher risk of resistance compared to combination therapy.

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