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Rare Parapneumonic Effusion Caused by Multidrug-Resistant *Cronobacter sakazakii*: A Case of Successful Treatment with Two-Week Course of Antibiotic Therapy

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Abstract

Introduction *Cronobacter sakazakii*, an opportunistic gram-negative bacillus, is known to induce meningitis in preterm infants, and enterocolitis and bacteremia in neonates and adults. However, the literature lacks documentation of parapneumonic effusion caused by this pathogen in adult patients. **Case Presentation** A 42-year-old male with a complex medical history, including chronic kidney disease, hypertensive cardiovascular disease, coronary artery disease, and type 2 diabetes mellitus, further complicated by a history of bilateral pleural effusion secondary to nephrosis requiring chest tube thoracostomy. He presented with a four-day history of productive cough and dyspnea. Initial evaluation and management focused on the fatal arrhythmia and subsequent encephalopathy, leading to intubation and extended hospitalization. The clinical course was further complicated by pneumonia and recurrence of pleural effusion, from which multidrug-resistant *C. sakazakii* was isolated using the conventional culture method. A two-week course of carbapenem and monobactam therapy yielded a favorable clinical outcome and resolution of the parapneumonic effusion. **Conclusion** This case report describes the first documented occurrence of multidrug-resistant *C. sakazakii*-induced parapneumonic effusion in a patient with complex comorbidities. Notably, a two-week antibiotic course effectively resolved the effusion, precluding the need for a more invasive surgical intervention.

Keywords

Cronobacter sakazakii, Parapneumonic Effusion, Multidrug-Resistant Bacteria, Case Report, Pleural Effusion, Adult Pneumonia, Opportunistic Infection

1. Introduction

Cronobacter, a genus of gram-negative, facultatively anaerobic, oxidase-negative, and catalase-positive bacillus within the Enterobacteriaceae family, represents an increasingly recognized opportunistic foodborne pathogen. While historically associated with meningitis, septicemia, necrotizing enterocolitis, and pneumonia in neonates and young infants [1] [2], recent surveillance data from the United States indicate a higher incidence of *Cronobacter* infections in adults, albeit with invasive disease and mortality disproportionately affecting infants. In adults, clinical manifestations typically encompass extra-intestinal infections such as urinary tract infections, septicemia, and pneumonia [1] [2] with additional reported presentations including osteomyelitis, wound infections, and splenic abscesses [3], particularly in elderly and immunocompromised individuals.

The ecological niche of *Cronobacter* species extends beyond powdered infant formula to encompass a wide array of foods and environmental sources, reflecting a broader global distribution than previously recognized [4]. This extensive dissemination is facilitated by *Cronobacter's* capacity to withstand extreme desiccation and high osmotic stress, a characteristic posited to contribute to its persistent presence in powdered infant formula manufacturing, other desiccated products, and arid environments [2] [5].

Epidemiologically, *C. sakazakii*, *C. malonaticus*, and *C. turicensis* are identified as the predominant pathogenic species, accounting for the majority of severe illnesses across all age demographics [2] [6]. While *C. sakazakii* infections in adults remain uncommon, a thorough review of existing literature revealed no previously documented cases of parapneumonic effusion caused by this pathogen in the Philippines and the world. This report, therefore, presents a rare occurrence of parapneumonic pleural effusion attributed to a multidrug-resistant *C. sakazakii* in an adult patient.

2. Objectives of the Study

2.1. General Objective

To present a rare case of parapneumonic effusion caused by a multidrug-resistant *C. sakazakii* in a 42-year-old male with multiple comorbid conditions

2.2. Specific Objectives

1) To describe the clinical manifestations associated with parapneumonic effusion caused by *C. sakazakii*.

2) To describe the diagnostic modalities, including imaging techniques and microbiologic identification.

3) To outline the therapeutic interventions, with specific emphasis on the antimicrobial regimens utilized in the management of the infection.

3. Significance of the Study

This case report presents a clinically challenging case of parapneumonic effusion

secondary to multidrug-resistant *C. sakazakii* infection. While bacterial pneumonia is a common antecedent of pleural effusion, this report highlights a causative agent that is 1). rarely observed in adults, and 2). characterized by high antimicrobial resistance yet responsive to medical therapy without surgical intervention. Furthermore, this report aims to elucidate the pathogenic potential of *C. sakazakii* beyond the neonatal population, thereby addressing a significant knowledge gap in the current literature. This report also aims to enhance the recognition and management of rare, drug-resistant pathogens among clinicians, with the goal of improving patient outcomes and informing treatment guidelines and antibiotic stewardship programs. Given the paucity of established guidelines for *C. sakazakii* infection, especially in the setting of high antimicrobial resistance, the findings of this case may serve as a valuable reference for clinicians managing similar cases where therapeutic options are constrained.

4. Case Presentation

A 42-year-old, Filipino, male, presented with a four-day history of productive cough, fever, chills, dyspnea, and hypoxemia. He was discharged two weeks prior following an admission for bilateral pleural effusion secondary to nephrosis, during which he underwent bilateral chest tube thoracostomy. He also received treatment for a complicated urinary tract infection with ceftriaxone and vancomycin. Upon discharge, the drains were noted to have clear serous output.

On further history, he has several comorbid conditions, including chronic kidney disease on maintenance hemodialysis, hypertension, type 2 diabetes mellitus, and active pulmonary tuberculosis requiring ongoing treatment.

Upon arrival at the emergency department, he presented with worsening dyspnea and hypoxemia. Within minutes, he became unconscious and unresponsive, necessitating immediate endotracheal intubation and resuscitation. Return of spontaneous circulation was achieved after three cycles. Post-resuscitation, bilateral coarse crackles were appreciated. A cranial computed tomography scan revealed no evidence of acute infarct or hemorrhage. A complete blood count demonstrated leukocytosis at 12,400 cells/μL. A chest radiograph shown in **Figure 1** showed bilateral pneumonia with minimal right-sided pleural effusion. He was managed for hypoxic-ischemic encephalopathy secondary to presumed fatal arrhythmia and community-acquired pneumonia with multidrug-resistant organism risk. Empiric therapy was initiated with meropenem and levofloxacin. Blood, endotracheal aspirate, and initial pleural fluid cultures yielded no microbial growth. Pleural fluid from the previously inserted chest tube thoracostomy drains remained clear. His lung infection demonstrated clinical improvement, and a repeat chest radiograph (**Figure 2**) after two weeks of antibiotics revealed interval regression of bilateral pneumonia. However, the pleural fluid from the chest tube thoracostomy became slightly turbid as shown in **Figure 3**. Due to limited therapeutic options resulting from the unavailability of newer cephalosporins and repurposed carbapenems in the hospital, the antibiotic regimen was changed to piperacillin/tazobactam and amikacin. Repeat pleural fluid cultures again did not demonstrate microbial growth.

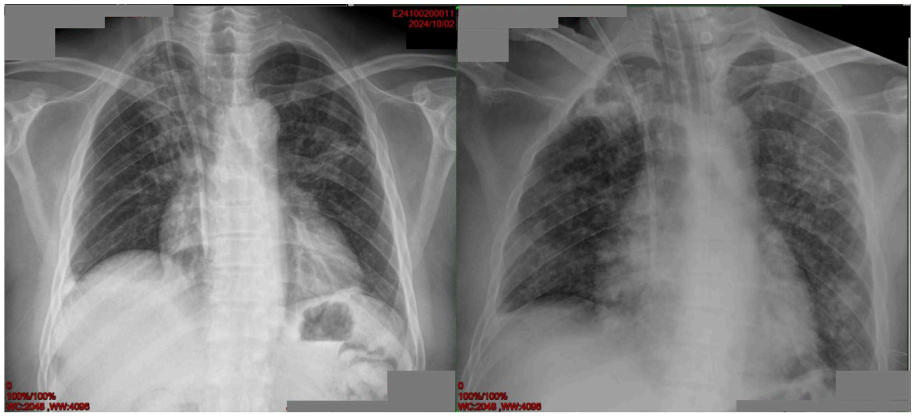

Figure 1. Radiographic comparison of chest radiograph: left panel, image from prior hospitalization; right panel, image from current admission. The right panel demonstrates hazy opacities in the mid-to-lower bilateral lung fields, consistent with pneumonia, and a minimal right-sided pleural effusion.

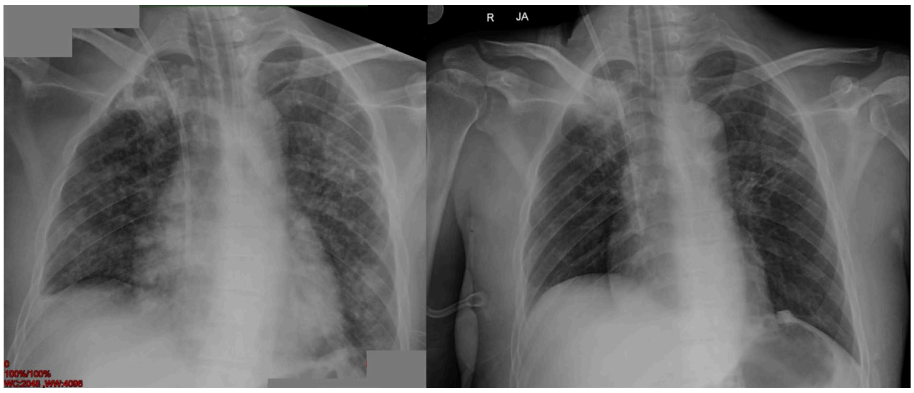

Figure 2. Radiographic comparison of chest radiographs: left panel, image from current admission; right panel, image following two weeks of antibiotic therapy (meropenem and aztreonam). The right panel demonstrates interval regression of hazy opacities within the bilateral mid-to-lower lung fields and resolution of the right-sided pleural effusion.

Figure 3. Right and left pleural fluid samples obtained from the chest tube thoracostomy exhibited increased turbidity.

Following five days of antibiotic therapy, the pleural fluid remained turbid. Subsequent pleural fluid cultures identified *C. sakazakii* (Figure 4), demonstrating resistance to amoxicillin-clavulanic acid, amikacin, cefepime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, ertapenem, gentamicin, imipenem, meropenem, piperacillin/tazobactam, and trimethoprim/sulfamethoxazole, with no reported antibiotic susceptibilities. Given the absence of established treatment guidelines for this multidrug-resistant isolate, recommendations for metallo-β-lactamase-producing Enterobacterales, specifically aztreonam/avibactam or ceftazidime/avibactam in combination with aztreonam [7] were considered. However, due to the unavailability of these agents in the hospital, meropenem 500 mg q24h and aztreonam 2 g q24h were administered, with dosages adjusted for renal function. After three days of this new antibiotic regimen, pleural fluid output from the chest tube thoracostomy decreased in volume and exhibited reduced turbidity. Repeat pleural fluid cultures as shown in Figure 5, performed after one week of antibiotics, yielded no microbial growth. Thoracic ultrasonography, performed after 14 days of antibiotics, as shown in Figure 6, revealed no evidence of pleural effusion, leading to the removal of both chest tube thoracostomy drains. A computerized chest tomography scan was also performed (Figure 7), which showed resolution of the bilateral pleural effusion.

Specimen Type	PLEURAL FLUID RIGHT JP DRAIN				
Organism Isolated	LIGHT GROWTH OF Cronobacter sakazakii group.				
Antimicrobial	**MIC**	**Interpretation**	**Antimicrobial**	**MIC**	**Interpretation**
Amikacin	>=64	R	Amoxicillin		
Amoxicillin/Clavulanic Acid	>=32	R	Ampicillin		
Benzylpenicillin			Cefepime	>=64	R
Cefoxitin	>=64	R	Ceftazidime	>=64	R
Ceftriaxone	>=64	R	Cefuroxime	>=64	R
Cefuroxime-Axetil	>=64	R	Ciprofloxacin	>=4	R
Clindamycin			Ertapenem	>=8	R
Erythromycin			Gentamicin	>=16	R
Gentamicin-High			Imipenem	>=16	R
Levofloxacin			Linezolid		
Meropenem	>=16	R	Moxifloxacin		
Nitrofurantoin			Oxacillin		
Piperacillin/Tazobactam	>=128	R	Quinupristin/Dalfopristin		
Rifampin			Streptomycin High Level (synergy)		
Tetracycline			Tigecycline		
Trimethoprim/Sulfamethoxazole	>=320	R	Vancomycin		
AES Findings					

Remarks: . PLEASE CORRELATE CLINICALLY.

Figure 4. Pleural fluid culture analysis yielded growth of multidrug-resistant *Cronobacter sakazakii*, with no reported antibiotic susceptibilities.

Specimen Type	PLEURAL FLUID JP DRAIN RIGHT				
Organism Isolated	NO GROWTH AFTER 48 HOURS OF INCUBATION UNDER AEROBIC CONDITION.				
Antimicrobial	**MIC**	**Interpretation**	**Antimicrobial**	**MIC**	**Interpretation**
Amikacin			Amoxicillin		
Amoxicillin/Clavulanic Acid			Ampicillin		
Benzylpenicillin			Cefepime		
Cefoxitin			Ceftazidime		
Ceftriaxone			Cefuroxime		
Cefuroxime-Axetil			Ciprofloxacin		
Clindamycin			Ertapenem		
Erythromycin			Gentamicin		
Gentamicin-High			Imipenem		
Levofloxacin			Linezolid		
Meropenem			Moxifloxacin		
Nitrofurantoin			Oxacillin		
Piperacillin/Tazobactam			Quinupristin/Dalfopristin		
Rifampin			Streptomycin High Level (synergy)		
Tetracycline			Tigecycline		
Trimethoprim/Sulfamethoxazole			Vancomycin		
AES Findings					

Remarks: . PLEASE CORRELATE CLINICALLY.

Specimen Type	PLEURAL FLUID JP DRAIN LEFT				
Organism Isolated	NO GROWTH AFTER 48 HOURS OF INCUBATION UNDER AEROBIC CONDITION.				
Antimicrobial	**MIC**	**Interpretation**	**Antimicrobial**	**MIC**	**Interpretation**
Amikacin			Amoxicillin		
Amoxicillin/Clavulanic Acid			Ampicillin		
Benzylpenicillin			Cefepime		
Cefoxitin			Ceftazidime		
Ceftriaxone			Cefuroxime		
Cefuroxime-Axetil			Ciprofloxacin		
Clindamycin			Ertapenem		
Erythromycin			Gentamicin		
Gentamicin-High			Imipenem		
Levofloxacin			Linezolid		
Meropenem			Moxifloxacin		
Nitrofurantoin			Oxacillin		
Piperacillin/Tazobactam			Quinupristin/Dalfopristin		
Rifampin			Streptomycin High Level (synergy)		
Tetracycline			Tigecycline		
Trimethoprim/Sulfamethoxazole			Vancomycin		
AES Findings					

Remarks: . PLEASE CORRELATE CLINICALLY.

Figure 5. Pleural fluid culture analysis, performed after one week of antibiotic therapy (meropenem and aztreonam), revealed the absence of microbial growth.

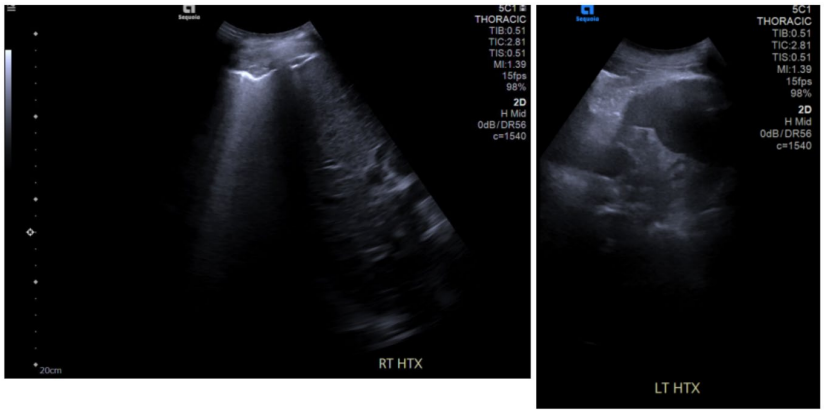

Figure 6. A thoracic ultrasound, performed two weeks following a course of meropenem and aztreonam, demonstrated complete resolution of previously observed bilateral pleural effusions

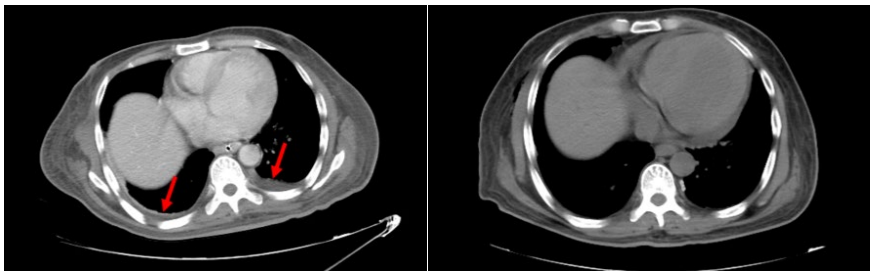

Figure 7. Radiographic comparison of computed chest tomography scans of the chest, left panel, image from previous admission; right panel, image following two weeks of antibiotic therapy (meropenem and aztreonam) and removal of thoracostomy tubes. The right panel shows interval resolution of pleural effusion.

The patient provided written informed consent for the publication of this case report.

5. Discussion

The incidence of pleural infection is increasing across both adult and pediatric

populations. However, the precise etiology remains undetermined. This observed rise may be attributable to enhanced clinical recognition and advancements in diagnostic modalities, including thoracic ultrasonography and computed tomography [8]. Established risk factors for pleural infection encompass pre-existing parenchymal lung disease [9], surgical interventions, trauma, and iatrogenic procedures such as prior thoracentesis [10]. Hospital-acquired pleural infections exhibit significant disparities from community-acquired cases in epidemiology, microbiology, and therapeutic strategies. Notably, hospital-acquired infections are associated with elevated mortality and prolonged convalescence compared to community-acquired infections [11].

Significant heterogeneity is observed in the microbiological etiology of hospital-acquired versus community-acquired pleural infections. In community-acquired cases, the most frequently isolated pathogens include the *Streptococcus intermedius* group (24%), *Streptococcus pneumoniae* (21%), other streptococcal species (7%), anaerobic bacteria (20%), and staphylococci (10%). In contrast, hospital-acquired infections are predominantly associated with staphylococci (35%) and gram-negative bacteria (23%), with methicillin-resistant *Staphylococcus aureus* (MRSA) representing 25% of these cases. The incidence of streptococcal infections is markedly reduced in the hospital environment, leading to a bacterial profile that exhibits a higher prevalence of antibiotic resistance, particularly to standard pneumonia therapies. This disparity in microbial profiles contributes to the significantly higher mortality observed in hospital-acquired infections (47%) compared to community-acquired infections (17%) [8].

The etiology of hospital-acquired pleural infections often includes MRSA and multidrug-resistant gram-negative bacteria, notably carbapenem-resistant Enterobacteriaceae (CRE), thereby mandating the initiation of broad-spectrum empirical antimicrobial therapy. CRE constitutes a critical global health concern, given that carbapenems are frequently considered the ultimate therapeutic intervention for antibiotic-resistant gram-negative bacterial infections [7]. The selection of treatment modalities is limited and predicated on factors such as the severity of the infectious process, the antimicrobial susceptibility profile of the implicated pathogen, and the potential for drug-related adverse events. Historically, the management of CRE infections has relied upon antibiotics from the polymyxin class (e.g., colistin, polymyxin B) or aminoglycoside class (e.g., amikacin, tobramycin, gentamicin). Nevertheless, challenges related to therapeutic efficacy, pharmacokinetic properties, and toxicological profiles complicate their clinical application [12].

The principal mechanism underlying carbapenem resistance in Enterobacterales is the production of carbapenemases, which are classified according to the Ambler scheme as either metallo-β-lactamases (MBLs) belonging to class B or serine β-lactamases belonging to classes A and D. MBLs exhibit the ability to hydrolyze all bicyclic β-lactam antibiotics and serine β-lactamase inhibitors commonly utilized in human medicine, encompassing sulbactam, tazobactam, clavulanic

acid, avibactam, and vaborbactam. Notably, MBLs lack the capacity to hydrolyze monobactam antibiotics. The selection of optimal antimicrobial agents for the treatment of CRE infections presents a significant clinical challenge. Current therapeutic regimens typically involve the synergistic combination of ceftazidime/avibactam with aztreonam or the administration of cefiderocol. Although colistin, fosfomycin, tetracyclines, and aminoglycosides may demonstrate in vitro susceptibility, their clinical application is often restricted by either suboptimal bactericidal activity or significant toxicological profiles [7].

Epidemiological data indicate that *Cronobacter* infections predominantly affect infants, particularly those born prematurely, with reported clinical presentations encompassing necrotizing enterocolitis and invasive [13]. Among adult individuals, particularly those with compromised immune function, *C. sakazakii* infections have been observed, manifesting as a spectrum of clinical entities, including urinary tract infections, bacteremia, osteomyelitis, splenic abscesses, and wound infections [13] [14].

While a substantial number of reported *Cronobacter* infections are attributed to the consumption of contaminated reconstituted infant formula [15] the possibility of other transmission vectors cannot be excluded, as infections have also been observed in breastfed infants [16]. The presence of *C. sakazakii* has been confirmed in the human gastrointestinal tract, as well as in domestic and healthcare settings, laboratory samples, and a variety of food products [17] [18]. Current research efforts are directed toward the determination of the precise etiology and origin of *C. sakazakii*, a pathogen that historically posed diagnostic challenges, leading to its underreporting [4].

This report details the first documented case of parapneumonic effusion in humans caused by *C. sakazakii*. The patient's underlying comorbid illnesses, namely diabetes mellitus and chronic kidney disease, coupled with prolonged endotracheal intubation, are posited to have contributed to creating an environment conducive to opportunistic *C. sakazakii* proliferation in the lungs. Although previous research has identified *C. sakazakii* in various clinical specimens including sputum, tracheal aspirates, and bronchoalveolar lavage fluid, cannulae, and sputum [1], this is the first report linking the organism to parapneumonic effusion in humans. This finding suggests a potential role for *C. sakazakii* in the etiology of pneumonia and subsequent pleural effusion in susceptible individuals. The culture of the pleural fluid yielded a multidrug-resistant strain of *C. sakazakii*. A treatment regimen consisting of a carbapenem and a monobactam resulted in a notable clinical recovery.

While *Cronobacter* species are typically susceptible to a broad range of antimicrobial agents, rendering antibiotic therapy generally effective [4] [14] [19], the emergence of antibiotic resistance poses a significant clinical challenge. Isolates exhibiting resistance to older-generation antibiotics, such as cephalothin, streptomycin, gentamicin, and tetracycline, have been identified [20]. Moreover, resistance to ampicillin and first- and second-generation cephalosporins has been

increasingly reported [4]. Historically, treatment strategies often relied on ampicillin in combination with gentamicin or chloramphenicol [4] [14]. However, given the documented resistance patterns, current therapeutic guidelines advocate for the use of third-generation cephalosporins or carbapenems (as an alternate treatment) in conjunction with aminoglycosides or trimethoprim/sulfamethoxazole [4] [14]. In particular, carbapenems have shown robust activity against *C. sakazakii*, an organism frequently displaying resistance to ampicillin and most cephalosporins [21].

The emergence of multidrug-resistant *C. sakazakii*, as observed in this case, poses a substantial challenge to clinical management. Carbapenems, frequently employed as a final therapeutic option for hospital-acquired infections caused by multidrug-resistant gram-negative pathogens, are experiencing diminished effectiveness due to the escalating global spread of resistant bacteria, particularly within the Enterobacterales [22]. The increasing prevalence of CRE, notably in the Middle East and Mediterranean region [23], underscores this concern. In the current case, the patient's complex clinical profile, characterized by multiple comorbid illnesses and a history of extensive antibiotic exposure, aligns with established risk factors for CRE. Prior antibiotic exposure, regardless of specific carbapenem use, has been documented as a significant predictor of non-carbapenemase-producing CRE development [24]. Furthermore, the patient exhibited numerous recognized risk factors, including healthcare exposure, intensive care unit admission, mechanical ventilation, dialysis, and the presence of indwelling catheters [25], all of which contributed to the heightened risk of acquiring a multidrug-resistant infection.

Individuals with significant comorbid conditions, prolonged hospitalizations, and a history of invasive procedures exhibit an elevated risk of MBL infections. While recent carbapenem administration within the preceding 30 days also contributes to this risk, its impact is comparatively less pronounced than that observed for non-carbapenemase-producing CRE [26]. Therapeutic options for infections caused by these organisms are severely constrained, primarily relying on last-line antimicrobial agents such as colistin and, more recently, the novel β-lactam-β-lactamase inhibitor combinations meropenem/vaborbactam and ceftazidime/avibactam [27]. A recent investigation demonstrated the efficacy of ceftazidime/avibactam in combination with aztreonam against resistant Enterobacter isolates, revealing *in vitro* synergism [28]. MBLs possess the capacity to hydrolyze all β-lactam antibiotics, with the exception of aztreonam. However, in MBL-producing Enterobacterales, aztreonam susceptibility is frequently compromised by co-produced β-lactamases. Consequently, aztreonam monotherapy maintains efficacy against approximately one-third of MBL isolates. The combination of aztreonam with a β-lactam/β-lactamase inhibitor, such as ceftazidime/ avibactam, restores aztreonam activity against MBLs, thereby presenting a potentially valuable therapeutic strategy [29]. In this case, the initial recommendation was to start on aztreonam/avibactam or aztreonam plus ceftazidime/avibactam. However, due to

the unavailability of these agents in the hospital, meropenem and aztreonam were administered instead. Consistent with the preceding rationale, the combination therapy utilizes aztreonam to counteract MBL-mediated resistance and meropenem to mitigate the impact of potential concurrent ESBL production, effectively restoring aztreonam's activity against MBLs. After two weeks of treatment with this combination, the patient improved. The application of carbapenems in the management of metallo-β-lactamase (MBL) infections is constrained by limited clinical evidence [30]. Given in vitro data, the lack of substantial clinical support, and the accessibility of alternative antimicrobial agents, prudent antibiotic stewardship dictates that carbapenem monotherapy.

6. Conclusion

This case report describes the first documented occurrence of multidrug-resistant *C. sakazakii*-induced parapneumonic effusion in a patient with complex comorbidities. Notably, a two-week antibiotic course effectively resolved the effusion, precluding the need for a more invasive surgical intervention.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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