

Cefepime-Induced Neutropenia: A Case Report and Literature Review

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Abstract: Cefepime is a fourth-generation cephalosporin utilized in treatment of multiple Gram-negative and -positive infections. The current report presents a case of 50-year-old man admitted with epidural abscess who developed neutropenia after prolonged use of cefepime. The neutropenia developed after 24 days of cefepime treatment and resolved 4 days after cessation of cefepime. Assessment of the patient's profile indicated no other possible cause for neutropenia. A literature review was done, and is presented herein to compare and identify the pattern of cefepime-induced neutropenia in 15 patients. The data presented in this article highlight that despite its rarity, cefepime-induced neutropenia should be considered by clinicians when planning a prolonged course of cefepime.

Keywords: neutropenia, cefepime, cephalosporin, adverse event, epidural abscess

Introduction

Neutrophils are an integral part of host defense mechanisms. They constitute the largest amount of white blood cells (WBCs), reaching up to 60% in the adult body.¹ Neutropenia is defined as a reduction in absolute neutrophil count (ANC; product of WBC and percentages of segmented and banded neutrophils) to <1500 cell/mm³. Neutropenia can be categorized as mild (1000–1500 cell/mm³), moderate (500–1000 cells/mm³), or severe (<500 cells/mm³).² Severe forms of neutropenia (ANC <100 cells/mm³) are simultaneously termed agranulocytosis, a life-threatening condition that usually manifests with severe infectious presentation.³ Mechanisms behind neutropenia include reduced production or differentiation in the bone marrow and peripheral destruction by immunological or cytotoxic mechanisms.^{2,4}

Neutropenia can be the product of a primary (congenital) or secondary (acquired) causes. Drug-induced neutropenia (DIN) is believed to be one of the main causes of acquired neutropenia and was first described in 1931.¹ In 1991, an incidence of four cases/million population/year was reported in a nationwide study.¹ With the expansion in the production of medical agents, the incidence of DIN has noticeably increased. Drugs implicated in $>50\%$ of the DIN reports include carbimazole, clozapine, dapsone, dipyrrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine.^{4,5}

Cefepime, a fourth-generation cephalosporin and β -lactam, is used in the treatment of Gram-positive and -negative bacteria that are susceptible to its activity. It is commonly used in the treatment of pneumonia, urinary tract infections, skin infections, and intra-abdominal infections, as well as an empirical antibiotic in management of febrile neutropenia.⁶ Common adverse reactions associated with cefepime use are gastrointestinal reactions, including *Clostridioides difficile* infection and neurotoxicity, including encephalopathy, aphasia, and seizure activities.⁷ One suspected DIN was encountered in the Qatar Rehabilitation Institute (QRI) and attributed to cefepime use. This report aims to document an encountered case of cefepime-induced neutropenia (CIN), describe the management approach, and review the available literature on CIN.

Case Presentation

A 50-year-old Filipino gentleman with a medical history of stroke, hypertension, diabetes, and diabetes-related kidney disease (baseline serum creatinine 150–200 $\mu\text{mol/L}$) presented to the emergency department with a history of fever of 5 days and low-back pain of 10 days. Low-back pain was worse with movement. On examination, he was afebrile, with tenderness in the lumbar area and no features of spinal cord or root compression.

Routine laboratory tests showed Hgb 12.8 g/dL, WBC count $26 \times 10^3/\mu\text{L}$, ALP 356 U/L, serum creatinine 211 $\mu\text{mol/L}$, CRP 189.3 mg/L, and sterile blood cultures. Medications administered regularly during his hospital stay were amlodipine 10 mg daily, atorvastatin 20 mg daily, carvedilol 6.25 mg twice daily, enoxaparin 40 mg daily, esomeprazole 40 mg daily, linagliptin 5 mg daily, sodium bicarbonate 1200 mg three times daily, paracetamol–orphenadrine 450/35 mg and tramadol 50 mg as needed for pain. His spine MRI showed an epidural collection at L5–S1 that measured approximately $40 \times 10 \times 8$ mm maximum, meningeal thickening, and edematous changes involving L5 and S1 vertebrae, along with L4/5 paraspinous and psoas abscess. He was started on ceftriaxone 2 g once daily, which was continued for 6 days, and then escalated to piperacillin–tazobactam as fever persisted. He underwent L1/2 and L5/S1 right-side laminotomy and drainage of epidural abscess. Pus and tissue were sent for culture, which turned out to be sterile and negative for TB.

Four days after the surgery, antibiotics were optimized to cefepime 2 g every 12 hours in view of the meningeal involvement seen on MRI and operation. Dosage was calculated based on adjusted body weight and creatinine clearance (48 mL/min). The plan was to continue cefepime for 6 weeks and then repeat imaging studies. His fever subsided after the surgery. CRP decreased to a quarter of the peak value and WBC count normalized in 1 week postsurgery (Table 1). After 4 weeks on cefepime, his WBC count started to decrease, reaching a nadir of 1400 cells/mm³ with ANC of 200 cells/mm³ (14%). These were accidental findings during routine blood tests, and the patient reported no symptoms associated with the marked changes in his WBC count. No changes in red blood cell count, Hgb, or platelet count were noted (Table 1). A diagnosis of CIN was considered, cefepime discontinued, and meropenem 2 g every 8 hours initiated. Dosage was calculated based on creatinine clearance (53 mL/min). Withdrawal of cefepime showed an immediate effect on lab results: WBC count increased to 2000 cells/mm³ and normalized to 4200 cells/mm³ within 4 days, with a similar response from neutrophils (Table 1, Figure 1). His treatment course was completed with meropenem, with no further adverse events.

Discussion

CIN is a rare side effect (<1%) that has been reported in postmarketing surveillance studies.^{8–13} In the presented case, culture results did not yield any bacterial colonies; however, the antimicrobial regimen was switched to cefepime for better distribution of medicine to the infected site. The patient had experienced a significant improvement on subsequent lab work (WBC and CRP) and spinal CT, which showed a marked reduction in abscess size. As noted in Figure 1, during the 30 days of treatment, there was a gradual decrease in WBC and ANC until they reached critical levels. The patient reported no complaints or symptoms accompanying the drop in WBC levels. After discontinuation of cefepime, there was a marked elevation in WBC and ANC levels within 4 days. The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 7 for the suspected incident, indicating a probable adverse drug event.¹⁴

DIN induced by antibiotics is considered an uncommon side effect, but is well-documented in the literature. A recent systematic review of 83 reports on antibiotic-induced neutropenia reported penicillin to be the most common class associated with the development of DIN (32%), followed by glycopeptides (28%), and non-penicillin β -lactams (19%). Among the antibiotics, vancomycin (n=24) and ceftaroline (n=12) were the most commonly reported to induce neutropenia. Only four cases of CIN were documented.¹⁵

DIN can be categorized into two categories based on the triggering agent. First, neutropenia can develop with the use of cytotoxic agents, immunosuppressants, or radiotherapy. This detrimental effect is dose-dependent and can be predicted by their pharmacological actions, which involve DNA damage and myelosuppression.³ Alternatively, noncytotoxic drugs have been observed to lead to idiosyncratic neutropenic reactions (also termed “bizarre” reactions), as they occur only rarely. As opposed to the former agents, no clear dose dependence has been observed.³ Despite the lack of clearly defined mechanisms for idiosyncratic DIN, research suggests that it is highly consistent with an immunomediated reaction.^{3,16,17}

Table I Lab results during cefepime therapy

Date	WBC (cells/mm ³)	ANC (cells/mm ³)	CRP (mg/L)	Hgb (g/dL)	MCV (fL)	Platelet (×10 ⁹ /L)	Urea (mmol/L)	Serum creatinine (μmol/L)	AST (U/L)	ALT (U/L)
30/08/2022 (day 1)	24,700 H	22,000 H	55 H	6.7 L	88.8	517 H	27.5 H	208 H	48	100 H
31/08/2022 (day 2)	20,600 H	17,300 H		7.7 L	88.2	328	25.5 H	207 H	19	57
01/09/2022 (day 3)	13,800 H	11,000 H		7.2 L	87.6	339			42	73
02/09/2022 (day 4)	10,100 H	7400 H		7.2 L	87.6	312	11.2 H	167 H	46	55
05/09/2022 (day 7)	9800 H	7600 H		7.9 L	87.8	316	7.9 H	151 H	49	85
13/09/2022 (day 15)	7300	5800		9.2 L	87.5	262	6.3	193 H	16	31
14/09/2022 (day 16)	5200	3700	21 H	9.1 L	85.8	278	5.4	176 H	17	26
22/09/2022 (day 24)	1800 L	600 L	13.1 H	10.1 L	85	224	4.9	175 H	19	17
28/09/2022 (day 30)	1400 C	500 C	85.7 H	10.5 L	84.9	243	4.1	159 H	18	15
29/09/2022	2000 L	200 C		9.8 L	83	265				
30/09/2022	2300 L	900 L		10.3 L	83.6	278				
01/10/2022	3600 L	2000		10.1 L	85.2	287				
02/10/2022	4200	2700	15.1 H	10.7 L	83.9	339				
06/10/2022	4800	3400	5.6 H	11.3 L	82.2	312	4.4	158 H	18	13

Abbreviations: H, high; L, low; C, critical.

The immunoresponse can be triggered by the drug acting as an antigen or more probably by its active metabolite acting as a hapten (a small molecule incapable of eliciting an immunoresponse unless it binds covalently with an endogenous protein), the resultant structural change in the protein — hypothesized to be neutrophil glycoprotein-drug complex — can lead to T-cell activation and formation of antibodies that lead to neutrophil destruction. Another hypothesized immunomediated reaction involves generating “danger signals” that lead to upregulation of inflammasomes, which activates a second signal for T-cell activation.¹⁷

Complications related to neutropenia include opportunistic infections, sepsis, and increased risk of mortality.^{1,2,4} A systematic review evaluating case reports of non-chemotherapy drug-induced neutropenia concluded that patients who had a nadir of <100 cells/mm³ had a significantly higher risk of local infections (59% vs 39%), sepsis (20% vs 6%), and fatal complications (10% vs 3%) than patients with a nadir of >100 cells/mm³ ($p<0.001$).⁴ In the presented case, the nadir reached 200 cells/mm³ with no reported signs or symptoms of local or systemic infections. Compared to available case reports in the literature (Table 2), five of 14 cases reported fever or flulike symptoms, one reported back pain, while eight were reported as asymptomatic.^{9–13}

Considering other potential causes of neutropenia, the patient’s medical record did not raise suspicion of other medications that would lead to an adverse event of neutropenia. Additionally, at the time of switching to cefepime, no other medicine was initiated concurrently, as all other medications were started since admission, so it is unlikely that neutropenia was induced by an alternative agent. Only three of the identified case reports mentioned the use of concurrent medications (Table 2), which included amikacin,^{9,10} cloxacillin,⁹ trimethoprim–sulfamethoxazole,⁹ ofloxacin, and

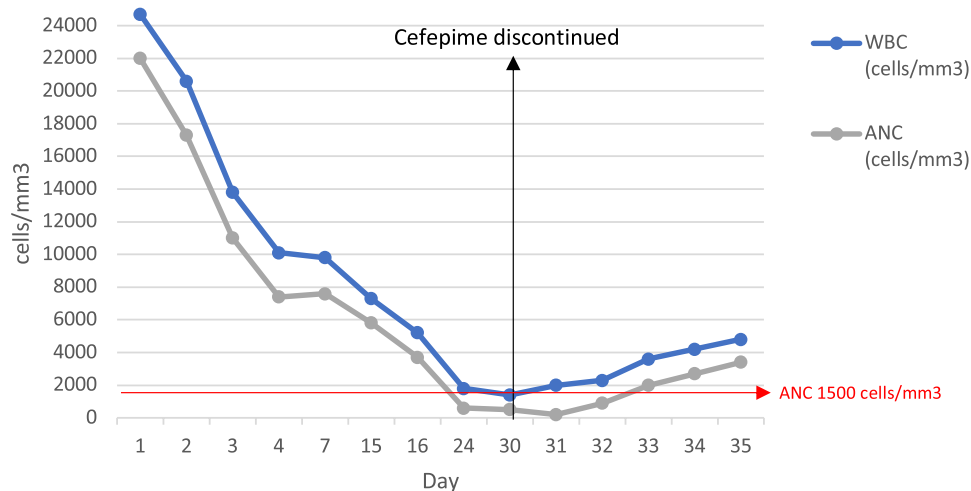


Figure 1 Patient's lab results during cefepime therapy. Cefepime was discontinued on day 30.

hydrocodone–acetaminophen.¹³ Both cloxacillin and co-trimoxazole have been reported as potentially inducing neutropenia,^{5,18,19} therefore, whether cefepime or the concomitant use of these antibiotics were the potential lead to neutropenia cannot be ruled out.⁹ Our patient received piperacillin–tazobactam for 4 days and then switched to cefepime for optimization of bioavailability due to meningeal involvement. While there are ample studies associating piperacillin–tazobactam with DIN,¹⁵ the hypothesized immunomediated mechanism of action for DIN indicates a delayed onset of reaction after initiation (ie, 1–6 months, a necessary period for the expansion in number of pathological T-cells).³ Available literature reports a median of 20 days of treatment until neutropenia develops with piperacillin–tazobactam,¹⁵ and the patient received his doses for 4 days before switching to cefepime.

Some studies have associated the rapid IV infusion of β -lactams with the development of neutropenia.^{8,20} In a retrospective study, a cluster of CIN during outpatient parenteral therapy was studied.⁸ Of the 168 who took cefepime, nine satisfied the CIN definition and all of them received cefepime for ≥ 2 weeks. It was noticed that patients who received cefepime as IV push were 7.42 times as likely to develop CIN. In the current report, the patient received cefepime in a standard infusion over 30 minutes. Further research is needed to evaluate a plausible physiological basis for the effect of infusion rate on development of neutropenia.

Available reports include patients who had osteomyelitis (n=9),^{12,13} surgery-related infections (n=3),^{10,11,13} or cystic fibrosis (n=2).⁹ Of the 14 cases, only three reported susceptible *Pseudomonas aeruginosa*^{9,10} and one susceptible *Serratia marcescens*;¹¹ however, the other nine cases were diagnosed with osteomyelitis,^{12,13} and cefepime is a mainstay of empiric therapy in the management of osteomyelitis.²¹ In the collated reports, the average time to neutropenia was 24 days (16–30) and the average time to recovery 6 (3–7) days, similar to what is described in this report (Table 1).

Emerging cross-reactivity studies support the substitution to an alternative β -lactam from a different group in cases of adverse events; however, this strategy in the setting of DIN is still under scrutiny, given the noted recurrence of neutropenia in 15%–30% of cases who are reintroduced to antibiotics.²² These data mainly include reintroducing the same agent (ie, rechallenging) or substituting to an agent with a structural similarity, which does not contradict the use of alternative antibiotics with different side chains or structure, as they are believed to be the main contributors to cross reactivity amongst β -lactams.²³ One case report of ceftriaxone-induced neutropenia reported complete resolution after substituting with cefepime. Despite them sharing R₁ side chain and core structure, they differed in the R₂ side chain, which was used to justify the absence of DIN recurrence.²⁴ In the present case, meropenem was initiated as an alternative antibiotic agent, and neutropenia resolved without any medical intervention or noted recurrence, similar to 12 of the cases presented in Table 2.

Interestingly, filgrastim (a colony-stimulating factor) was initiated in two cases to aid the resolution of neutropenia.¹² The reports mentioned no difference in duration to recovery, as opposed to the available literature. A systematic review

Table 2 Summary of case reports on cefepime-induced neutropenia

Case #	Date	Age (years)	Sex	Dose/regimen	Indication	Baseline WBC	Baseline ANC	Time to neutropenia (days)	WBC level	Neutropenia level	Clinical status	Action taken	Time to recovery (days)
1	2022	50	Male	Cefepime 2 g q12h	Epidural abscess	7300	5800	24	1400	200	Asymptomatic	Discontinued cefepime, started meropenem	4
2	2010 ⁸	2	Female	Cloxacillin (50 mg/kg/dose every 6 h), cefepime (50 mg/kg/dose every 8 h) and amikacin (30 mg/kg once daily)	Cystic fibrosis respiratory exacerbation (<i>S. aureus</i> and <i>P. aeruginosa</i>)	9310	5030	16	1800	43	—	Discontinued cloxacillin and cefepime, started levofloxacin 20 mg/kg IV	6
3		4	Male	Cotrimoxazole (6 mg/kg/dose q8h) cefepime (50 mg/kg/dose every 8 h) and amikacin (20 mg/kg once daily)	Cystic fibrosis respiratory exacerbation (<i>P. aeruginosa</i>)	12,500	9000	20	2530	700	—————	Discontinued cefepime	3
4	2010 ⁹	15	Male	Cefepime 2 g IV q12h Amikacin 1 g IM q24h	Purulent discharge following surgical intervention to right ankle. Carbapenem-resistant <i>P. aeruginosa</i>	4800–6200	—	24	1100	39	Asymptomatic	Whole therapy discontinued	7
5	2008 ¹⁰	16	Female	Cefepime IV (113 mg/kg/day, divided into three doses)	Postoperative <i>Serratia marcescens</i> wound infection (spinal fusion following motor vehicle collision)	7300	4110	19	1070	20	Asymptomatic	Discontinued cefepime. Replaced by vancomycin (42 mg/kg/day divided into three doses) and ciprofloxacin (23 mg/kg/day divided into two doses)	5

(Continued)

Table 2 (Continued).

Case #	Date	Age (years)	Sex	Dose/regimen	Indication	Baseline WBC	Baseline ANC	Time to neutropenia (days)	WBC level	Neutropenia level	Clinical status	Action taken	Time to recovery (days)
6	2003 ¹¹	27	Male	Cefepime IV	Osteomyelitis	3700–10,300	5700	26	–	800	Flulike symptoms (n=4), including fever and chills Back pain (n=1)	Discontinued cefepime (n=5) Discontinued cefepime, started a 300 µg dose of filgrastim (n=1) Continue cefepime, start filgrastim (n=1) Completed cefepime (n=1)	7
7		31	Male				6300	25		400			
8		22	Male				4700	30		300			
9		42	Male				4000	26		1500			
10		34	Male				3400	23		1400			
11		18	Male				4700	25		1400			
12		30	Male				11,000	26		200			
13		18	Male				4500	17		600			
14	1997 ¹²	42	Male	Cefepime 2 g IV q12h	Osteomyelitis	7600	5090	29	1700	119	Asymptomatic	Discontinued cefepime Metronidazole IV 500 mg q12h and aztreonam IV 2 g q8h	7
				Ofloxacin PO 200 mg q12h									
15		48	Female	Cefepime 2 g IV q12h	Infected open wound following motorcycle accident	5500	2915	30	1500	150	Chills and fever 103f	Discontinued antimicrobial therapy 6 days earlier than planned	4

Note: WBC and ANC in cells/mm³.

of case reports with acute antibiotic-induced neutropenia conducted a subgroup analysis of 50 cases after 1991, reporting a statistically significant reduction in the median duration of neutropenia when using a colony-stimulating factor compared to no treatment (median 7.0 vs 3.5 days, $p=0.017$).¹⁵

Recommendations

The results of this case and the other reports summarized in this work indicate the need for including complete blood count and differentials in the routine workup (eg, twice weekly) for patients starting a long course of cefepime. In terms of case reporting, several gaps have been identified that led to challenges in assessing and collating the data, eg, none of the case reports assessed causality. Authors utilizing the Adverse Drug Reaction Probability Scale would aid in standardizing the assessment of causality.¹⁴ Additionally, a comprehensive presentation of patients' laboratory data would be a great asset in identifying patterns of deterioration or resolution, as well as concurrent effect on other blood cells. Clear description of concurrent medications (ie, agents, start time, frequency, and duration) is essential to assess the certainty and probability of the hypothesized agent being the true culprit. Future research may be aimed at studying the prevalence of CIN in Qatar and potential risk factors of the development of CIN, including an ethnicity-based epidemiological study, which could shed light on the possibility of DIN risk being attributed to patients' ethnicity and genetic differences.

Conclusion

The presented case report signifies potential adverse reactions associated with prolonged use of cefepime. Available literature highlights its rarity as a side effect; however, clinicians must exercise caution and be aware of CIN as a possibility with prolonged use of cefepime to prevent complications associated with neutropenia.

Ethics

This report was approved by the Medical Research Center (MRC) at Hamad Medical Corporation (HMC) in 2022 (MRC-04-22-688). Informed consent for publication of the patient's deidentified case details was obtained from the patient before submission.

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Disclosure

The authors report no conflicts of interest in this work.

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