JPPT | Case Series

Use of Granulocyte-Colony Stimulating Factor for Beta-Lactam Induced Neutropenia in Children With Bacterial Meningitis

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Drug induced neutropenia is an uncommon but potentially serious side effect in children receiving prolonged β-lactam antibiotic therapy. Management of β-lactam induced neutropenia in children remains challenging and often requires antibiotic therapy interruption or modification. There are limited data in pediatric patients about use of granulocyte-colony stimulating factor (G-CSF) for the treatment of drug induced neutropenia. We report the use of G-CSF for β-lactam induced neutropenia in four pediatric patients between the ages of 3 months and 18 years with bacterial meningitis in this case series.

ABBREVIATIONS ANC, absolute neutrophil count; CSF, cerebrospinal fluid; G-CSF, granulocyte-colony stimulating factor; IV, intravenous; LP, lumbar puncture; VP, ventriculoperitoneal; WBC, white blood cell

KEYWORDS β-lactam; bacterial meningitis; granulocyte-colony stimulating factor; neutropenia

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Introduction

Beta-lactam antibiotics are commonly prescribed for the treatment of bacterial meningitis in children. However, prolonged courses of β-lactam antibiotics (>14 days) increase the risk of drug-induced neutropenia.[1–3] Although β-lactam induced neutropenia is a relatively uncommon side effect, early identification of the etiology of the neutropenia and management can be challenging. Delayed management can lead to the development of complications including life-threatening infections.[4] Multiple case reports in adults describe use of granulocyte-colony stimulating factor (G-CSF) for decreasing the duration of β-lactam-induced neutropenia and improving clinical outcomes.[3,5–7] Discontinuation of the offending agent or changing antibiotic therapy to another agent (β-lactam or non-β-lactam) remains the primary management of β-lactam induced neutropenia in children given the lack of data describing use of G-CSF in pediatric patients for this indication.[1,3] We report our experience using G-CSF for β-lactam induced neutropenia in children with bacterial meningitis in this case series.

Methods

We included patients that were admitted to Texas Children's Hospital between 2012 and 2023 with a diagnosis of bacterial meningitis using ICD-10 codes[8], who received a β-lactam antibiotic and at least one dose of G-CSF. Neutropenia was defined as absolute neutrophil count (ANC) <1500 cells/mm^3 as institutional preference. Patients with neutropenia from other sources were excluded.

Results

Fifty-three patients with bacterial meningitis were identified through ICD-10 codes and medical record chart review. Of those 53 patients, 48 patients were excluded for not receiving G-CSF during the treatment course for meningitis and 1 patient was excluded due to underlying hematologic condition (congenital neutropenia). Of note, no adverse events related to G-CSF administration were noted during chart review.

Case 1

In 2012, a 2-year-old 12.2 kg girl with history of extreme prematurity, necrotizing enterocolitis, and hydrocephalus requiring a ventriculoperitoneal (VP) shunt was admitted with fever, lethargy, clumsiness, and abnormal eye movements. Cerebrospinal fluid (CSF) was obtained from lumbar puncture (LP) and shunt fluid; the VP shunt was removed and an external ventricular drain was placed. Cerebrospinal fluid revealed a white blood cell (WBC) count of 361 cells/mm^3 (87% neutrophils, 11% lymphocytes) and elevated protein of 2928 mg/dL. She received intravenous (IV) vancomycin 15 mg/kg per dose every 6 hours and cefotaxime 75 mg/kg per dose every 6 hours as empiric antibiotic therapy for meningitis. Cerebrospinal fluid cultures from all sampled sites grew *Streptococcus pneumoniae* susceptible to penicillin and cefotaxime. She continued

therapy with cefotaxime alone. Despite negative repeat cultures from the ventricles, she continued to experience seizure episodes and intermittent fever. Cefotaxime was discontinued on day 9 of treatment and the patient received IV penicillin 100,000 units/kg per dose every 6 hours with gentamicin 2.5 mg/kg per dose every 8 hours from days 9 to 13. Since day 13, antibiotic therapy was narrowed to IV penicillin alone and the patient remained clinically stable and afebrile with slowly down-trending WBC and ANC values.

On day 28 of antibiotic treatment, the peripheral blood ANC was 190 cells/mm^3. She was given a one-time dose of filgrastim 5 mcg/kg subcutaneously (SQ). On day 29, the patient's ANC improved to 730 cells/mm^3 and antibiotic therapy was changed to cefotaxime and vancomycin from penicillin due to hemodynamic changes concerning for new hospital-acquired infection including infection of the VP shunt. Vancomycin was discontinued on day 30 of therapy after repeat CSF cultures were sterile from a newly placed VP shunt. The ANC from day of therapy 30 also increased to 1900 cells/mm^3. She completed cefotaxime on day 42 of therapy, and the ANC continued to increase and remained above 1500 cells/mm^3.

Case 2

A 4-month-old 8.5 kg boy with history of Erb palsy was admitted for fever, increased fussiness, and seizure in 2012. A lumber puncture showed CSF with 2399 cells/mm^3 WBC (92% neutrophils, 5% lymphocytes) and elevated protein of 108 mg/dL. He received IV cefotaxime 75 mg/kg per dose every 6 hours, vancomycin 15 mg/kg per dose every 6 hours, acyclovir 15 mg/kg per dose every 8 hours, and gentamicin 2.5 mg/kg per dose every 8 hours as empiric antibiotic therapy. Acyclovir was discontinued on day 3 of treatment after confirmation of negative herpes simplex virus polymerase chain reaction test result from CSF fluid. Cerebrospinal fluid culture grew *Escherichia coli* (*E coli*) susceptible to third generation cephalosporins. The antibiotic regimen was narrowed to cefotaxime monotherapy on day 8 of treatment. He continued to have persistently elevated inflammatory markers, C-reactive protein of 13.1 mg/dL and erythrocyte sedimentation rate of 108 mm/hr, on day 9 of treatment without resolution of subdural empyema on the subsequent magnetic resonance imaging findings also on day 9 of treatment.

Between days 21 and 24 of cefotaxime monotherapy, his ANC decreased from 2840 to 760 cells/mm^3 and further decreased to 380 cells/mm^3 on day 28. He received 2 doses of filgrastim 10 mcg/kg SQ daily on days 29 and 30, and the ANC was 8250 cells/mm^3 on day 31; however, on day 36 of treatment, the ANC decreased to 340 cells/mm^3 and a one-time dose of filgrastim 5 mcg/kg was given SQ. The ANC rebounded to 9840 cells/mm^3 the next day and remained above 1500 cells/mm^3 while continuing cefotaxime. He received 42 days of IV antibiotics and was discharged home.

Case 3

An 18-year-old, 65.5 kg previously healthy male was transferred from an outside hospital for surgical management of CSF infection again in 2012. He initially presented for evaluation after 5 days of frontal headache with neck stiffness and 2 days of fever. Cerebrospinal fluid from LP showed 926 cells/mm^3 WBC (63% neutrophils, 3% lymphocytes). Severe pansinusitis and epidural abscess fluid collections were noted from head imaging. He underwent craniectomy/craniotomy for empyema drainage and received IV cefotaxime 2000 mg every 4 hours, metronidazole 500 mg every 6 hours, and vancomycin 1000 mg every 6 hours. Cultures obtained during the surgery, and CSF cultures from both institutions did not grow any pathogens. Vancomycin was initially discontinued on day 6 of treatment, and the patient remained on cefotaxime and metronidazole. The patient continued to experience frontal headaches, intermittent fever, and seizure episodes on cefotaxime and metronidazole resulting in resuming vancomycin on day 9 of treatment. Antibiotic therapy was narrowed again to cefotaxime and metronidazole on day 13 of treatment.

The patient's ANC decreased from 6030 to 560 cells/mm^3 between days 19 and 26 with a nadir of 30 cells/mm^3 on day 29. He received filgrastim 5 mcg/kg SQ daily on days 32 and 33, and the ANC increased to 7510 cells/mm^3 on day 34. He remained clinically stable and was discharged home after completing 42 days of IV antibiotics.

Case 4

A 3-month-old, 13.2 kg previously healthy female was admitted in 2023 for fussiness and low-grade fever. No antibiotics were initiated at that time. On hospital day 2, she had increased irritability, and a LP was performed with CSF results as follows: WBC 1615 cells/mm^3 (57% neutrophils, 21% lymphocytes), Gram-negative rods on Gram stain, and bacteria present. She empirically received IV ceftriaxone 50 mg/kg per dose every 12 hours and gentamicin 2.5 mg/kg per dose every 8 hours. Later that day, the patient had seizure episodes and developed fever. On day 4 of hospitalization, ceftriaxone was changed to IV ceftazidime 50 mg/kg per dose every 8 hours and gentamicin was continued pending susceptibilities. Cerebrospinal fluid cultures grew *E coli,* and brain magnetic resonance imaging demonstrated ventriculitis and bilateral subdural empyemas. On hospital day 5, repeat CSF was obtained and showed 140 WBC/mm^3 (67% neutrophils, 22% lymphocytes). The CSF culture grew *E coli* susceptible to ceftriaxone, ceftazidime, and meropenem but resistant to gentamicin. Ceftazidime and gentamicin were discontinued and ceftriaxone was resumed. She developed fever

Table. Summary of Cases

Case	Age, Sex	Infection (etiology)	Definitive Therapy	Baseline WBC ($\times 10^3/\mu L$)	Baseline ANC cells/ mm^3	Total Treatment Duration (days)	Time to Neutropenia (<1000 cells/ mm^3) (days)	G-CSF Therapy	Day of treatment and ANC at time of G-CSF	Time to ANC Improvement
1	2 yr, F	Bacterial meningitis (*S pneumoniae*)	Penicillin IV 100,000 units/kg/ dose Q6H	24.09	16,480	42	19	5 mcg/kg SQ once	Day 28: 190	2
2	4 mo, M	Bacterial meningitis (*E coli*)	Cefotaxime IV 75 mg/ kg/dose IV Q6H	13.2	9320	42	1st occurrence: 19	10 mcg/ kg SQ daily for 2 days	Days 29 and 30: 380	1
							2nd occurrence: 36	5 mcg/kg SQ once	Day 26: 340	1
3	18 yr, M	Pansinusitis and subdural empyema (unknown)	Cefotaxime 2000 mg Q4H	20.02	18,680	68	26	5 mcg/kg SQ daily for 2 days	Day 29: 30	2
4	3 mo, F	Ventriculitis and bilateral subdural empyema (*E coli*)	Ceftriaxone IV 50 mg/ kg/dose IV Q12H	8.01	2120	68	32	5 mcg/kg SQ once	Day 47: 100	1

F, female; M, male; SQ, subcutaneously

and new seizure episodes on day 10 of hospitalization, and cultures were obtained with drainage of one of the subdural empyemas. The culture grew *E coli*. The patient continued to receive ceftriaxone monotherapy. Ceftriaxone was changed to IV meropenem 40 mg/kg per dose every 8 hours on day 28 of hospitalization after the patient developed hypotension requiring vasoactive agents and increased episodes of seizures.

Neutropenia developed on hospital day 31, and the ANC continued to drop and remained <500 cells/mm^3 between day 32 to 41 with a nadir of 100 cells/mm^3 on day 47. Filgrastim 5 mcg/kg SQ was administered on day 47. The patient's ANC improved to 3160 cells/mm^3 the following day. She remained clinically stable without further seizure episodes, and her ANC remained above 1500 cells/mm^3 until day 66 (1008 cells/mm^3). No G-CSF was given, as therapy was stopped on day 68 of antibiotics with no ANC between days 66 and 68. She was discharged home after completing 68 days of treatment.

Discussion

The majority of the β-lactam induced neutropenia episodes in adult patients are associated with prolonged exposure to IV β-lactam antibiotic courses, especially in those receiving more than 2 weeks of treatment. Certain β-lactam antibiotics such as penicillin G, nafcillin, oxacillin, piperacillin-tazobactam, ceftriaxone, and ceftaroline have been reported to cause more neutropenia episodes compared with other agents.[3,4,7] The incidence of β-lactam induced neutropenia in pediatric patients varies significantly among published studies. A systematic review by Battini et al[1] identified 2602 pediatric patients who received antibiotic courses and 228 patients who developed neutropenia episodes during therapy. The most commonly administered antibiotics were penicillin, amoxicillin, ampicillin, β-lactam/β-lactamase inhibitors, and cephalosporins. Our pediatric patients that developed neutropenic episodes received cefotaxime, ceftriaxone, cefepime, and penicillin G, among other agents (Table).

The mean onset of β-lactam induced neutropenia in our patients was 26 days, which was similar to the timing reported in adults but was longer when compared with case studies in other pediatric patients (range of median values 10–23 days).[1–3,9]

In pediatric patients, the current primary management of β-lactam induced neutropenia includes discontinuing the offending antibiotic agent, reducing the dose, withholding the antibiotic for 24 to 48 hours or changing therapy in addition to close monitoring. Some clinicians recommend interruption of the offending antibiotic therapy when the ANC is <1000 cells/mm^3 due to the potential for serious complications associated

with severe neutropenia (ANC <500 cells/mm).[3,10,11] It is crucial to monitor patients' ANC closely and determine the appropriate time to interrupt the antibiotic therapy in the setting of other confounding comorbidities and/or medications. Battini et al[1] noted that among 228 patients all less than 18 years old with β-lactam induced neutropenia, 77 had therapy discontinued while others achieved normalization of the ANC without any interventions.[1] Data regarding the use of G-CSF to decrease the duration of neutropenia is mainly from critically ill adult patients.[3,5–7] Our cohort of patients received G-CSF at doses between 5 and 10 mcg/kg SQ daily and their ANCs rebounded to >1000 cells/mm^3 within the following 2 days. None of the patients had any adverse effects reported from G-CSF use. Since G-CSF directly stimulates the creation and maturation of neutrophil precursors, the response seen in our cohort matches the reported onset of action in the package insert.[12]

However, use of G-CSF may increase patient costs and risk of adverse events that also may require treatment (e.g., nausea, pain, fever, etc), and there are no current data evaluating the benefits of using G-CSF in children with meningitis and β-lactam-induced neutropenia compared with the previously mentioned risks. Given this lack of data, we suggest to consider giving G-CSF in this population when other treatment options do not exist due to patient contraindications and/or resistance patterns of the pathogens.

We cannot draw significant conclusions from our small number of patients at a single institution. However, our case series provides a basis for considering G-CSF administration in pediatric patients who develop β-lactam-associated neutropenia during prolonged antibiotic treatment for bacterial meningitis, especially when other treatment options are limited or unavailable. A larger study is needed to evaluate the role of G-CSF in β-lactam induced neutropenia in children with meningitis and other severe infections requiring long courses of β-lactam antibiotics.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant international guidelines on human experimentation and have been approved by the appropriate committees at our institution. However, given the nature of this study, informed consent was not required by our institution.

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References

1. Battini V, Mari A, Gringeri M, et al. Antibiotic-induced neutropenia in pediatric patients: new insights from pharmacoepidemiological analyses and a systematic Review. *Front Pharmacol*. 2022;13:877–932.
2. Olson SC, Smith S, Weissman SJ, Kronman MP. Adverse events in pediatric patients receiving long-term outpatient antimicrobials. *J Pediatric Infect Dis Soc*. 2015;4(2):119–125.
3. Cimino C, Allos BM, Phillips EJ. A review of β-lactam-associated neutropenia and implications for cross-reactivity. *Ann Pharmacother*. 2021;55(8):1037–1049.
4. Holz JM, Chevtchenko AV, Aitullina A. Acute antibiotically induced neutropenia: a systematic review of case reports. *Br J Clin Pharmacol*. 2022;88(5):1978–1984.
5. Vial T, Bailly H, Perault-Pochat MC, et al. Beta-lactam induced severe neutropaenia: a descriptive study. *Fundam Clin Pharmacol*. 2019;33(2):225–231.
6. Andrès E, Maloisel F, Zimmer J. The role of haematopoietic growth factors granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in the management of drug-induced agranulocytosis. *Br J Haematol*. 2010;150(1):3–8.
7. Aung, ZY, Elmagraby K, Nica A. Neutropenia induced by ceftriaxone and meropenem. *Eur J Case Intern Med*. 2024;11(7):004593.
8. *International Classification of Diseases*. 10th rev. World Health Organization; 1994.
9. Gomez M, Maraqa N, Alvarez A, Rathore M. Complications of outpatient parenteral antibiotic therapy in childhood. *Pediatr Infect Dis J.* 2001;20(5):541–543.
10. Koraysh S, Koleri J, Ali M. Cefepime-induced neutropenia: a case report and literature review. *Clin Pharmacol*. 2023;15:33–40.
11. Curtis BR. Non-chemotherapy drug-induced neutropenia: key points to manage the challenges. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):187–193.
12. Neupogen (filgrastim) [product monograph]. Thousand Oaks, CA: Amgen, Inc; 2023.