

# Agranulocytosis from Outpatient Antimicrobial Treatment with Ceftriaxone: A Case Report

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## ABSTRACT

**Introduction:** Agranulocytosis from antimicrobial therapy with ceftriaxone is rare. We report a case of agranulocytosis resulting from ceftriaxone noted more than 3 weeks into therapy.

**Case Presentation:** A 72-year-old woman who was started on ceftriaxone for septic arthritis of the left knee 3 weeks before presentation was admitted to the hospital after being found to be neutropenic on outpatient laboratory analysis. Her absolute neutrophil count on admission was 0/μL. The cause of the agranulocytosis was suspected to be ceftriaxone. The drug was stopped, and she was started on granulocyte colony-stimulating factor with gradual resolution of the neutropenia.

**Discussion:** Serious adverse effects of ceftriaxone therapy, such as agranulocytosis, must be monitored for, especially in patients who are receiving prolonged therapy or high doses. Once this cause of agranulocytosis is identified, ceftriaxone therapy should be stopped; if the patient is febrile, an infectious disease workup should be performed and antibiotics should be started; and granulocyte colony-stimulating factor should be administered with daily monitoring of the absolute neutrophil count.

## INTRODUCTION

Ceftriaxone is the most commonly used agent in outpatient parenteral antimicrobial therapy.<sup>1</sup> It has a half-life that permits for daily dosing, thus making it a preferred agent for outpatient use. It is generally safe and well tolerated, with data showing that ceftriaxone-induced leukopenia occurs in 0.09% of the courses administered.<sup>1</sup> We report a rare case of agranulocytosis resulting from ceftriaxone noted more than 3 weeks into therapy.

## CASE PRESENTATION

### Presenting Concerns

A 72-year-old woman with bilateral total knee arthroplasties presented to the Emergency Department after being found to be neutropenic on outpatient laboratory analysis. The patient had been admitted 1 month earlier because of pain and swelling in her left knee and was found to have septic arthritis of the joint. She underwent irrigation and débridement with revision of the polyethylene insert. Wound cultures yielded methicillin-sensitive *Staphylococcus aureus*. She was discharged on a regimen of ceftriaxone, 2 g daily, via a peripheral indwelling catheter. Her absolute neutrophil count (ANC) several days before discharge, and 1 day before starting ceftriaxone

treatment, was 7221/μL. She continued receiving ceftriaxone for the next 3 weeks and was then found to have an ANC of 165/μL on outpatient bloodwork.

Her symptoms on presentation were pain in the left knee, dysgeusia, and diarrhea. Physical examination findings were unremarkable. A complete blood cell count showed white blood cells of 900/μL and an ANC of 0/μL. A peripheral blood smear showed no neutrophils or blast cells, normocytic red blood cells with mild anisocytosis and no target cells or schistocytes, and a normal platelet count without clumps. Results of an infectious disease workup, including blood cultures, urine culture, and chest x-ray film, were normal. Stool samples were negative for *Clostridium difficile* toxin, *Giardia* and *Cryptosporidium* organisms, and ova and parasites. Erythrocyte sedimentation rate was 84 mm/h, and C-reactive protein was 1.7 mg/dL. Hepatitis B surface antigen was negative, hepatitis C antibody was negative, and HIV antigen/antibody was negative. Antinuclear antibody titer was less than 40. Folate and vitamin B<sub>12</sub> levels were normal. Thus, infectious, rheumatologic, and nutritional deficiency causes of neutropenia were ruled out. Results of a radiograph of the left knee noted only mild soft-tissue edema.

## Therapeutic Intervention and Treatment

The cause of the agranulocytosis was suspected to be drug induced from ceftriaxone, with an adverse drug reaction probability (Naranjo) score of “probable.”<sup>2</sup> Treatment with the medication was stopped, and the patient was started on an oral regimen of levofloxacin, 500 mg/d, and rifampin, 600 mg/d, to treat her prosthetic joint infection. In addition, treatment with filgrastim, a granulocyte colony-stimulating factor (G-CSF), was started, initially with 300 μg subcutaneously nightly.

## Follow-up and Outcomes

Because the patient’s ANC remained below 100/μL after 2 doses, the G-CSF dose was increased to 480 μg. She received an additional 2 doses at this strength, and her ANC increased to 4131/μL.

The patient was subsequently discharged home, with outpatient follow-up recommended. Table 1 presents a timeline of the case.

## DISCUSSION

Agranulocytosis, classically defined as a neutrophil count below  $0.5 \times 10^9/L$ , historically carried a mortality rate of 10% to 16%.<sup>3</sup> Although the mortality rate has improved to 5%, the condition is still considered life-threatening and is most dangerous in patients older than age 65 years and in those with renal failure, bacteremia, or shock at the time of diagnosis.<sup>3</sup>

A previously published review of case reports from 1966 to 2006 involving 980 patients with possible drug-induced

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agranulocytosis identified only 6 cases in which there was a probable relationship between the agranulocytosis and ceftriaxone.<sup>4</sup> In addition, a 2015 case report and literature review identified 13 published cases with a probable relationship between ceftriaxone and agranulocytosis.<sup>5</sup> Data from clinical trials show that neutropenia from ceftriaxone occurred in 3% of patients, but only in those receiving 2 g for 4 weeks.<sup>6</sup> This timeline is consistent with that of our patient, who presented with neutropenia after 25 days of 2 g of daily ceftriaxone therapy, and is similar to other reported cases.<sup>5,7</sup> Thus, it appears that higher doses and/or prolonged treatment with ceftriaxone is a risk factor for the development of agranulocytosis.

The management and treatment of drug-induced agranulocytosis begins with identification and cessation of the offending agent. If the patient is febrile, an infectious disease workup should be performed and broad-spectrum antibiotics should be started. A bone marrow biopsy was not performed in this case; however, performing one may be essential in cases where other cell lines are affected to rule out an underlying disease process.<sup>3</sup> A bone marrow biopsy may also help predict when to expect recovery of the neutrophil count.

**Key Learning Points**

Ceftriaxone is the most commonly used agent in outpatient parenteral antimicrobial therapy and is generally safe and well tolerated.

Agranulocytosis from ceftriaxone is rare, but higher doses of ceftriaxone (2 g to 4 g daily) and prolonged duration of therapy (average time of 23 to 25 days) appear to be risk factors.

Management involves cessation of ceftriaxone treatment and, if the patient is febrile, performing an infectious disease workup and starting antibiotics. Bone marrow biopsy can be considered. Granulocyte colony-stimulating factor should be administered and absolute neutrophil count monitored daily.

Rechallenge with the offending agent should be avoided if possible.

**Table 1. Timeline of the case**

Day	Event, diagnostic testing, and intervention
Prior admission	
Day -8 to 0	The patient was admitted to the hospital, underwent arthrocentesis with concern for septic arthritis of the left knee, then underwent irrigation and débridement with revision of polyethylene insert. She was started on a regimen of vancomycin and piperacillin-tazobactam. Her ANC on Day -1 was 7221/ $\mu$ L.
Day 0	Wound cultures yielded methicillin-sensitive <i>Staphylococcus aureus</i> . Antibiotics were changed, and the patient started on a ceftriaxone regimen.
Day 5	She was discharged from the hospital.
Day 25	Outpatient bloodwork showed an ANC of 165/ $\mu$ L.
Current admission	
Day 26	The patient was admitted to the hospital. She had an ANC of 0/ $\mu$ L.
Day 27	Infectious disease workup had normal results. Peripheral smear results showed no neutrophils and no blast cells. She was started on a regimen of levofloxacin, 500 mg/d orally; rifampin, 600 mg/d orally; and G-CSF, 300 $\mu$ g subcutaneously nightly.
Day 28	The patient had an ANC of 0/ $\mu$ L.
Day 29	The patient had an ANC of 38/ $\mu$ L. G-CSF dose increased to 480 $\mu$ g subcutaneously nightly.
Day 30	The patient had an ANC of 304/ $\mu$ L.
Day 31	The patient had an ANC of 4131/ $\mu$ L. She was discharged home.

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

If there is lack of myeloid precursors, recovery is unlikely before 14 days, and if there is maturation arrest, recovery is likely within 2 to 7 days.<sup>3</sup> Although neutrophil counts should improve once administration of the offending agent is stopped, G-CSF can be administered to decrease the time to resolution. The usefulness of G-CSF in drug-induced agranulocytosis has been investigated in the past, but with mixed results depending on the severity of the agranulocytosis.<sup>8,9</sup> The review of 980 patients with drug-induced agranulocytosis did not show a significant association between decreased case-fatality rates and G-CSF, but did find a significant association between shorter duration of neutropenia and G-CSF.<sup>4</sup> In our patient, who had severe agranulocytosis, the initial dose of G-CSF did not improve her ANC, but after the dose was increased, her ANC rapidly improved. However, this increase in ANC may have been seen in several days regardless of G-CSF dose escalation given that it has been shown that G-CSF causes neutrophil counts to recover in 6 to 12 days.<sup>10</sup> Thus, there appears to be a role for using G-CSF in patients with agranulocytosis, regardless of the severity, although it may take additional doses and several days to resolve the neutropenia in patients with severe agranulocytosis.

Regarding possibly rechallenging patients with the offending drug, there have been several published reports of patients being rechallenged with a drug that was suspected of causing neutropenia and subsequently experiencing neutropenia again.<sup>11,12</sup> Whitman et al<sup>13</sup> described a case of cefazolin-induced leukopenia in a patient who then experienced leukopenia again when given cefoxitin. They concluded that  $\beta$ -lactam antibiotics should be avoided if leukopenia caused by these drugs is suspected. However, Uy et al<sup>5</sup> described a case of ceftriaxone-induced neutropenia with improvement in the neutrophil count despite the patient being started on a cefepime regimen. We would recommend that our patient avoid future use of ceftriaxone. She will also probably need close monitoring should she require other  $\beta$ -lactam antibiotics.

**CONCLUSION**

We present a case of idiosyncratic drug-induced agranulocytosis attributed to ceftriaxone. Although ceftriaxone is frequently used in both the inpatient and outpatient setting, serious adverse effects, such as this one, must be monitored for, especially in patients who are receiving prolonged therapy or high doses. Once this cause of agranulocytosis is identified,

ceftriaxone therapy should be stopped; if the patient is febrile, an infectious disease workup should be performed and antibiotics should be started; and G-CSF should be administered, with daily ANC monitoring. ❖

#### Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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