Case Report

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Case Series of Ceftriaxone-Induced Neutropenia and Leukopenia: Experience in Outpatient Parenteral Antimicrobial Therapy (OPAT) Setting

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ABSTRACT

Ceftriaxone is a commonly used antibiotic to treat a range of infections, particularly for central nervous system, skin and soft tissues as well as bone and joint infections. The course length of ceftriaxone for these indications can range between 2 to 6 weeks in both hospital and outpatient parenteral antimicrobial therapy (OPAT) settings. With prolonged courses being used, coupled with the general understanding that beta-lactam antibiotics are safer than other classes of antibiotics, there is a need for increasing awareness of safety of ceftriaxone, particularly on rarer but more serious adverse effects, such as neutropenia and leukopenia, which may lead to clinical complications. This case series describes the identification of three cases of ceftriaxone-induced neutropenia and leukopenia in an OPAT setting, as well as patients' management and short-term outcomes following the event.

Abbreviations: OPAT: Outpatient Parenteral Antimicrobial Therapy; MHRA: Medicines and Healthcare Products Regulatory Agency; G-CSF: Granulocyte-Colony Stimulating Factor; NHS: National Health Service; CRP: C-Reactive Protein; FBC: Full Blood Counts; APER: Abdominoperineal Resection; MRI: Magnetic Resonance Imaging; ANC: Absolute Neutrophil Count; WBC: White Blood Cells

Introduction

Drug-induced neutropenia is a potentially serious and life-threatening adverse effect that may lead to severe complications, such as neutropenic fever [1], severe infections, intensive hospital treatments, withdrawal of critical medications, life-threatening morbidity, and even mortality [2]. Common classes of medications that are associated with causing neutropenia include antipsychotics, anticonvulsants, immunomodulators, chemotherapy drugs, antimicrobials and anti-malarials [1,3]. The incidence of non-chemotherapy idiosyncratic drug-induced neutropenia is reported to range from 2.4 to 15.4 cases per million people [4]. Among the reported cases of antibiotic-induced neutropenia, beta-lactams and glycopeptides are the most common reported causative agents [5-7]. The mechanism of antibiotic-induced neutropenia remains uncertain and potentially multifactorial. Studies suggest either an immunologically mediated reaction due to formation of anti-neutrophil antibodies [8] or a direct myelosuppressive effect of antibiotics evidenced by an increased myeloid precursor cells on bone marrow aspirates [9]. Ceftriaxone is a commonly used beta-lactam antibiotic in treating a range of infections, owing to its broad spectrum of microorganism coverage [10], option for once daily administration, and good distribution into the central nervous system, skin and soft tissues, as well as bones and joints [11].

Neutropenia and leukopenia are listed as common or very common side effects of ceftriaxone in the British National Formulary, while very severe neutropenia (agranulocytosis) is listed as rare or very rare [12]. Despite so, there are relatively few case reports published on ceftriaxone-induced neutropenia [13,14], especially in an outpatient parenteral antimicrobial therapy (OPAT) setting [15,16], where long courses of ceftriaxone, ranging from 2 to 6 weeks, are administered. The Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card interactive drug analysis shows that only 63 cases of neutropenia and 10 cases of leukopenia were reported between the 1989 and November 2023 [17], highlighting a need for increasing awareness of identifying and monitoring for ceftriaxone-induced neutropenia and leukopenia.

Definitions and Symptoms of Neutropenia and Leukopenia

Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1.5 x 10^9/L and graded as per (Table 1) [3]. Symptoms of neutropenia include fever, chills, sore throat, muscle and joint pain but patients could be asymptomatic at the time of severe neutropenia when detected, especially if the patient is monitored for early detection [18,19]. Sepsis can also be the presentation due to the abrupt onset of agranulocytosis [20,21]. Leukopenia is a reduction of white blood cells (WBC) count to less than 4 x 10^9/L [22]. It is usually the consequence of neutropenia, but may also be associated with the reduction of other leukocytes such as lymphocytes, monocytes, eosinophils or basophils. Leukopenia may not present with any symptoms. However, underlying conditions causing leukopenia or infections developing from leukopenia may present with symptoms such as fever, chills, sore throat, fatigue, infected wound, weight loss, enlarged lymph nodes, enlarged liver or spleen, small bruises on skin and mucosal bleeding [23].

Table 1: Severity grading of neutropenia based on definitions by Newburger, et al. [3].

Severity	Absolute Neutrophil Count	Potential Functional Consequences
Mild	1-1.5 x10^9/L	May not impair host defence, but warrant investigation of underlying cause
Moderate	0.5-1 x10^9/L	May slightly increase the risk of infections if the immune system is already impaired
Severe	0.2-0.5 x10^9/L	Increased risk of infections in most patients
Very severe (agranulocytosis)	<0.2x10^9/L	Risk of severe, life-threatening infections with susceptibility to opportunistic organisms

Treatment and Management of Drug-Induced Neutropenia and Leukopenia

According to the american society of haematology, the most important treatment of idiosyncratic drug-induced neutropenia is to withdraw the offending drug regardless of whether the patient is symptomatic. After the offending drug is removed, most cases of neutropenia resolve over time [18], the average time for full recovery of the neutrophil count is 9 days (range: 9-24 days) [24]. The use of granulocyte-colony stimulating factor (G-CSF) can be a treatment option especially for patients experiencing prolonged neutropenia [18]. Some reports showed the use of G-CSF can shorten the duration of neutropenia [25], antibiotic therapy (for treating infection caused by the neutropenia) and length of hospital stay [24]. Patients with neutrophil count < 0.1x10^9/L should receive G-CSF as it is associated with more infections and fatal complications [24]. Subcutaneous injection of 300micrograms/day is the commonly used dosage in treating adult patients with idiosyncratic drug-induced neutropenia. Regimen of 5 micrograms/kg/day until neutrophil counts recover above 0.5x10^9/L has also been recommended [26].

Case Descriptions

In this paper, the authors present 3 cases of ceftriaxone-induced neutropenia and leukopenia identified and managed on OPAT service in a rural National Health Service (NHS) Trust between December 2021 and May 2023. The first case involved an 80-year old Caucasian female patient presented with prosthetic joint infection following right total knee replacement. Her past medical history includes atrial fibrillation, chronic kidney disease, diverticular disease, bilateral total hip replacement, osteoporosis, osteoarthritis and anaemia. On admission, she developed stage 2 acute kidney injury with elevated C-reactive protein (CRP), WBC and neutrophils. She undergone knee aspiration on day 2 of admission and the fluid aspirate grew Group G Streptococcus. She received 3 days of intravenous (IV) flucloxacillin 2 gram four times daily, followed by one dose of IV piperacillin/tazobactam 4.5 gram, before her antibiotic was switched to IV ceftriaxone 2 gram once daily following first-stage right knee revision. She was referred to OPAT to complete six weeks of ceftriaxone. By day 29 of ceftriaxone, her renal function has returned to baseline of eGFR 83 mL/min. While waiting to start OPAT, she developed very severe neutropenia (agranulocytosis) and leukopenia on day 37 of ceftriaxone (Table 2). She was afebrile and her observations remained normal [National Early Warning Score (NEWS) 0].

Table 2: Time course of haematological indices for the first patient.

	White Blood Cells (10*9/L)	Neutrophils (10*9/L)	Lymphocytes (10*9/L)	Haemoglobin (g/L)	Platelets (10*9/L)
On admission (4 days pre-treatment)	20.4	19.01	0.34	102	210
Day 1 ceftriaxone	14.5	12.38	0.82	101	292
Day 7 ceftriaxone	15	12.67	1.23	86	360
Day 14 ceftriaxone	7.6	5.96	0.89	91	364
Day 29 ceftriaxone	4.6	2.85	1.02	88	291
Day 37 ceftriaxone (developed neutropenia and leukopenia; ceftriaxone stopped on the same day)	1.8	0.05	0.8	88	343
1 day after stopping ceftriaxone, day 1 IV flucloxacillin	1.9	0.19	0.93	88	359
5 days after stopping ceftriaxone, day 5 IV flucloxacillin (neutropenia and leukopenia resolved)	6.1	3.57	1.42	93	377
14 days after stopping ceftriaxone, day 14 IV flucloxacillin	7	4.8	1.3	88	322

Ceftriaxone was stopped on the same day and switched to IV flucloxacillin 2 gram four times daily on the next day. Haematology team was consulted, and the advice was to perform haematinics tests (vitamin B12, folate, ferritin and iron studies) and to check for full blood counts (FBC) on alternate days. Her vitamin B12 and folate were normal, and her ferritin was raised due to anaemia. Other drug- and infection-related causes of neutropenia and leukopenia were ruled out. Her neutropenia and leukopenia resolved five days following the withdrawal of ceftriaxone. She remained well and completed the remaining course of IV flucloxacillin without complications before being discharged from hospital. No clinical or biochemical complications were reported at 3-, 6-, 9- and 12-months following the incident. The second case involved a 69-year old Caucasian male patient who was admitted with sacral and rectal pain, intermittent fever and frequent night sweats following abdominoperineal resection (APER) procedure from six months ago. His past medical history includes hypertension, arthritis, anterior colonic resection, adenocarcinoma of rectum, and multiple pelvic collections since APER. On admission, his inflammatory markers (CRP, WBC and neutrophils) were raised and his haemoglobin was low. The magnetic resonance imaging (MRI) found a known pelvic collection and acute sacral osteomyelitis. He received 2 days of IV flucloxacillin and 5 days of IV amoxicillin before receiving computed tomography (CT)-guided drainage of the collection.

His antibiotic was switched to IV piperacillin/tazobactam and oral metronidazole for a total of 6 weeks based on sensitivity of Escherichia coli (E. coli) grown in the collection pus sample. After receiving 27 days of piperacillin/tazobactam, his antibiotics were switched to IV ceftriaxone 2 gram once daily and oral metronidazole for the remaining course to be completed on OPAT. While on OPAT, he developed mild neutropenia and leukopenia on day 8 of ceftriaxone treatment (Table 3) which were confirmed on blood film. He remained afebrile and well with normal observations (NEWS 0). His renal function was normal (eGFR> 90 mL/min) or close to normal (eGFR 84mL/min) on days leading to the development of neutropenia. He received ceftriaxone on day 8 prior to blood results being made available, and ceftriaxone was subsequently stopped on the same day and switched to IV ertapenem 1 gram once daily from the next day. As his lymphocytes were low, he was advised to take a lateral flow test for Coronavirus-19 (Covid-19) and the result was negative. Neutropenia induced by other drugs was ruled out as no new medications were started and none of his existing medications was known to cause neutropenia/leukopenia. His neutropenia and leukopenia resolved six days following the withdrawal of ceftriaxone. He remained well while receiving ertapenem for another 7 days before completing OPAT. No clinical or biochemical complications were reported at 3-, 6-, 9- and 12-months following the incident.

Table 3: Time course of haematological indices for the second patient.

	White Blood Cells (10*9/L)	Neutrophils (10*9/L)	Lymphocytes (10*9/L)	Haemoglobin (g/L)	Platelets (10*9/L)
4 days pre-treatment	6.5	4.94	0.78	97	445
Day 1 ceftriaxone	7.1	5.81	0.48	107	471
Day 8 ceftriaxone (developed neutropenia and leukopenia; ceftriaxone stopped on the same day)	2.6	1.22	0.85	100	316
1 day after stopping ceftriaxone, day 1 ertapenem	3.9	1.93	1.16	110	410
6 days after stopping ceftriaxone, day 6 ertapenem (neutropenia and leukopenia resolved)	4.8	2.94	1.06	104	333
13 days after stopping ceftriaxone	5.2	3.28	1.04	108	326

The third case involved a 87-year old Caucasian female patient who was repatriated from a neighbouring hospital with T4 and T5 spondylodiscitis and past medical history of angina, thoracic discitis, hypertension, polymyalgia rheumatic, Alzheimer's disease, bilateral cataracts, hypothyroidism and thyroidectomy due to thyroid cancer. Prior to repatriation, she had an episode of E. coIi bacteraemia for which she was treated with ciprofloxacin. Spinal multidisciplinary team advised she was not for surgery due to severe dementia and co-morbidities. She was started on IV ceftriaxone 2 gram once daily in the neighbouring hospital before being referred to the local OPAT service on day 23 of ceftriaxone. As MRI showed progression of spondylodiscitis, oral co-trimoxazole 960mg twice daily was added on day 24 of ceftriaxone. She started receiving OPAT in her care home on day 26 of ceftriaxone treatment. On day 30 of ceftriaxone (day 7 of co-trimoxazole), she developed severe neutropenia and leukopenia (Table 4) which were confirmed on blood film. On the same day, she developed stage 1 acute kidney injury (eGFR dropped from 86 to 68mL/min) due to dehydration secondary to several episodes of loose stools. Her CRP increased from 54 to 117mg/L and her NEWS score was 1 due to low systolic blood pressure. Care home reported she looked well otherwise. Haematinic tests were performed and came back to be normal. Given her loose stool episodes from several days ago and rising CRP, care home was advised to send off stool sample to test for Clostridium difficile if she develops loose stools again.

Table 4: Time course of haematological indices for the third patient.

	White Blood Cells (10*9/L)	Neutrophils (10*9/L)	Lymphocytes (10*9/L)	Haemoglobin (g/L)	Platelets (10*9/L)
6 days pre-treatment	8.8	7.22	0.8	119	354
Day 1 ceftriaxone	10.7	9.25	0.82	120	386
Day 23 ceftriaxone	6.6	5.3	0.79	122	207
Day 30 ceftriaxone, day 7 co-trimoxazole (developed neutropenia and leukopenia	2.1	0.37	0.97	115	234
Day 32 ceftriaxone (co-trimoxazole stopped and oral ciprofloxacin started)	1.9	0.09	0.96	112	286
Day 34 ceftriaxone, day 3 oral ciprofloxacin	1.7	0.12	0.7	106	300
Day 37 ceftriaxone, day 6 oral ciprofloxacin (ceftriaxone stopped on the same day)	1.6	0.02	0.71	99	309
1 day after stopping ceftriaxone (continuing oral ciprofloxacin)	2	0.04	1.03	108	363
4 days after stopping ceftriaxone (received first dose of G-CSF)	2.8	0.21	1.53	103	333
5 days after stopping ceftriaxone (received second dose of G-CSF; neutropenia and leukopenia resolved)	9.4	5.59	2.44	109	191
6 days after stopping ceftriaxone (admitted into hospital with sepsis)	24	19.34	2.59	121	379
On discharge (treated with 7 days of piperacillin/tazobactam)	9.4	7.18	1.17	126	218

As oral co-trimoxazole was started more recently, it was first considered the plausible cause of neutropenia and leukopenia. Ceftriaxone was continued, and oral co-trimoxazole was stopped and switched to oral ciprofloxacin 400mg twice daily on day 3 of neutropenia. On day 33 of ceftriaxone (day 4 of neutropenia), care home reported patient developed tachypnoeic and low-pitched expiratory wheezing, without shortness of breath or cough. Her observations were increased to 4-hourly monitoring in care home. Covid-19 lateral flow test result was negative. Despite stopping oral co-trimoxazole, she developed agranulocytosis on day 32 of ceftriaxone treatment and her neutrophils continued to worsen over 5 days period. As the neutrophils and WBC did not recover over 5-day period after stopping co-trimoxazole, ceftriaxone was now considered the most likely cause of neutropenia and leukopenia, and it was eventually stopped on day 37 of treatment (day 8 of neutropenia) while oral ciprofloxacin was continued as monotherapy. She was admitted onto ambulatory care on day 9 of neutropenia for clinical assessment to rule out other sources of infections and causes of neutropenia. Haematology advice was sought and she was started on 300 microgram once daily of G-CSF before being discharged back into the care home. Her neutropenia and leukopenia resolved following two doses of G-CSF. However, she became unwell with abdominal pain and loose stools the next day after her neutrophils and WBC recovered, and she was admitted into the hospital.

Chest X-ray suggested lower respiratory tract infection and electrocardiogram showed prolonged QTc interval. Ciprofloxacin, memantine and sertraline that are known to cause QTc prolongation were stopped. Stool sample was not tested for Clostridium difficile as they were semi-formed stools. She received seven days of IV piperacillin/tazobactam for sepsis and responded well. She was discharged back to the care home on end-of-life pathway and passed away 5 weeks later.

Discussion

In this case series, the onset of neutropenia from the initiation of ceftriaxone varied between individuals, being day 37 (first case), day 8 (second case) and day 30 (third case), respectively. All three patients received 2 gram once daily regimen, and therefore dose-dependent effect was not examined in this paper. However, there are publications that suggest dose-dependent inhibition of granulopoiesis by ceftriaxone through formation of anti-neutrophil antibodies [27]. Two patients developed very severe ceftriaxone-induced neutropenia (agranulocytosis), while one patient developed mild neutropenia. All three cases of ceftriaxone-induced neutropenia and leukopenia were reversible following the withdrawal of ceftriaxone, where the first two patients recovered from neutropenia after 5 and 7 days of stopping ceftriaxone, respectively, while the third patient required G-CSF treatment. The third case highlights particular challenges in identifying ceftriaxone as the offending drug when patients receive concurrent medications that may also cause neutropenia and/or leukopenia. In the third case, ceftriaxone was not initially considered the cause of neutropenia as patient had more recently started on co-trimoxazole. Ceftriaxone was continued for another seven days before being stopped and the accumulative effect of inhibition of granulopoiesis may have explained the need for G-CSF to reverse the neutropenia and leukopenia, as well as the subsequent development of infection due to neutropenia.

Potential drug-drug interactions between ceftriaxone and other medications leading to neutropenia have also been reported [28]. These findings highlight the importance of regular full blood count monitoring while patients receive ceftriaxone, as well as good history taking and medication reconciliation while on OPAT, to ensure the causative agent(s) can be identified and withheld as early as possible in the event of neutropenia and/or leukopenia. Following the cessation of ceftriaxone, all three patients tolerated beta-lactam antibiotics, namely flucloxacillin, ertapenem and piperacillin/tazobactam, respectively, without developing abnormalities to full blood count. As the mechanism of beta-lactam induced neutropenia remains uncertain, controversy exists on cross-reactivity and future use of alternative beta-lactam antibiotics. Several studies suggest that alternative beta-lactam with differing side chains should not be considered contraindicated following beta-lactam-induced neutropenia [29-32]. This is supported by the authors' observation in this case series, where patients tolerated penicillins and carbapenems that carry different R1 and R2 side chains from ceftriaxone. As beta-lactam antibiotics are effective for a range of infections, consideration should be given on clearly documenting ceftriaxone- or specific beta-lactam-induced neutropenia in health records, such that the documentation does not prevent patients from accessing alternative beta-lactam antibiotics when needed. Educational drive targeting at both clinicians and patients should be embedded into the national penicillin allergy delabelling initiative [33] to improve understanding on accurate documentation of ceftriaxone- and other drug-induced adverse events, as well as the treatment options available following the events.

In terms of short-term outcome, the first two patients did not present with clinical or biochemical complications within 12 months of recovering from neutropenia. The third patient developed an episode of chest infection shortly after recovering from neutropenia, therefore the chest infection was potentially a complication of ceftriaxone-induced neutropenia, with increased risk due to the delay in identifying the offending drug in patients who receive concurrent medications that could also cause neutropenia and/or leukopenia.

Conclusion

This case series highlights the importance of monitoring full blood count as well as the risk of neutropenia and/or leukopenia while patients receive ceftriaxone treatment, particularly for prolonged treatment in both inpatient and OPAT settings. Good history taking and medication reconciliation help to identify and/or rule-out concurrent medications that may cause or contribute to the development of neutropenia and/or leukopenia, leading to timely management of idio-

syncratic drug-induced neutropenia. Having a clear escalation route in managing ceftriaxone-induced neutropenia and leukopenia in an OPAT setting will mitigate the risks of clinical complications and ensure therapeutic effectiveness in infection management.

Author Contributions

- Sue Wen Leo: Conceptualisation; investigation; data analysis and interpretation; writing – original draft; review and editing.
- Sze Wing Fok: Investigation; writing – original draft; review and editing.
- Swapna Motukupally: Review and editing.
- Karen Fan: Review and editing.
- Freeman Wu: Review and editing.

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Conflicts of Interests

The Authors declare that there are no competing interests.

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