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Clozapine-Associated Neutropenia With COVID-19 Infection and the Role of Filgrastim

Devender Singh Yadav

Heatherwood Court Hospital, Pontypridd, UK

Correspondence: Devender Singh Yadav (dryadav.devender@gmail.com)

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ABSTRACT

Clozapine is the gold standard, evidence-based treatment of choice for treatment-resistant schizophrenia. However, clozapine can induce serious, life-threatening adverse effects, including neutropenia and agranulocytosis. There is accumulating evidence to suggest that rechallenging with clozapine should be considered in most patients with clozapine-associated neutropenia (mild to moderate neutropenia) who do not respond to other treatments. Ruling out other causes of coincidental neutropenia is important when the neutropenia occurs after 2 years of treatment on clozapine, as the risk of developing neutropenia becomes negligible after 2 years and becomes nonspecific to clozapine. When our patient developed neutropenia whilst taking clozapine during Covid-19 infection, she benefitted from Filgrastim [a Granulocyte-Colony Stimulating Factor (G-CSF)], which provided symptomatic treatment.

1 | Introduction

Clozapine is effective in treating refractory cases of schizophrenia and schizoaffective disorder [1]. However, it can be associated with serious, life-threatening adverse effects, including neutropenia and agranulocytosis. Despite this, overall mortality may be lower for those on clozapine than in schizophrenia, possibly because of its antisuicidal effect. It is estimated that around 2.9% of patients treated with clozapine develop neutropenia, and around 0.4%–0.8% of clozapine treated patients develop agranulocytosis [2, 3].

Most serious neutropenia leading to clozapine cessation occurs within 18 weeks of treatment and becomes negligible after 2 years [4]. This early drop in neutrophil count before 2 years is strongly tied to the clozapine drug's mechanisms or patient genetics and is not coincidental.

It is possible that clozapine is not the causative agent in some cases of coincidental neutropenia [5]. Ruling out other causes of coincidental neutropenia (e.g., COVID-19 infection or other viral/bacterial, benign ethnic neutropenia, other co-prescribed medications [antipsychotic medications, sodium valproate, proton pump inhibitors]) is important after 2 years of treatment with clozapine as the risk of developing neutropenia drops significantly and becomes nonspecific to clozapine.

Although, the risk of neutropenia and agranulocytosis is highest in the first 3 months, this may occur at any time, even after years of treatment [6, 7]. Our patient had developed clozapine-associated neutropenia after 13.5 years.

Patients who experience neutropenia with clozapine are at an increased risk of developing neutropenia on rechallenge. Hence, rechallenging a patient who previously experienced neutropenia with clozapine is a difficult clinical decision [8].

There is accumulating evidence to suggest that rechallenging with clozapine should be considered in most patients with clozapine-associated neutropenia (mild to moderate neutropenia) who do not respond to other treatments. A more careful risk–benefit analysis is needed in cases of clozapine-associated agranulocytosis (severe neutropenia) [9].

In selected patients, cases of clozapine associated neutropenia can be managed with either Lithium or Colony-Granulocyte Stimulating Factor (C-GSF). These decisions should be made

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based on the patient's unique circumstances, after a thorough risk-benefit analysis, discussions with the stakeholders involved in the patient's care, and close monitoring is essential.

When our patient developed neutropenia whilst taking clozapine during Covid-19 infection, she benefitted from Filgrastim [a Granulocyte-Colony Stimulating Factor (G-CSF)].

The G-CSF was given for a short period of time; this provided symptomatic treatment and allowed continuation of clozapine.

2 | Case Presentation

A 39-year-old lady with an extensive forensic history, who had spent most of her adult life in institutional care, having graduated from Child and Adolescent Mental Health Services (CAMHS); she had an established diagnosis of paranoid schizophrenia.

Clozapine was started in August 2007 for treatment-resistant schizophrenia.

After a prolonged journey in secure forensic hospitals, she eventually stepped down to a community-supported placement in 2018 and maintained a relatively good quality of life at the supported accommodation in the community, up until February 2021.

Between March 2020 and April 2020, the patient had 5 amber results, followed by 2 amber results in November 2020, followed by an amber result on 11 February 2021. In between, she had green results on FBC (full blood count) monitoring. All amber results were due to low neutrophils.

- *26th of February 2021: 1.4 Neutrophils*
- *3rd of March 2021: 1.4 Neutrophils*

The ZTAS (Zaponex Treatment Access System), who monitored the clozapine opined that the patient is 'non-re-challengeable' for clozapine due to the Two 'Red Results' as noted above.

A deterioration was noted after the clozapine was stopped in March 2021 leading to re-admission to the hospital, due to escalating risks. She was recalled from her CTO (community treatment order) and was admitted to an inpatient unit in March 2021.

The patient had received clozapine for around 13.5 years.

After a stay in a psychiatric intensive care unit (PICU), she was moved to a Locked Rehab Hospital in November 2022, and she was subsequently admitted to our low secure unit (LSU) on 24 March 2022, under Section 3 of the MHA (Mental Health Act). She was very unwell, presenting with florid psychosis and continued risks to herself and others. The MDT (multidisciplinary team) found it difficult to manage her risks. The prescribed antipsychotic and other prescribed medications for her agitated behaviours were not making much difference.

A second opinion was sought from the NPU (national psychosis unit, London), who assessed her on 16 January 2023, and submitted their report in February 2023. As per the recommendations from the NPU, the patient could be re-challenged on clozapine.

To safeguard the patient, opinion was sought from the SOAD (second opinion appointed doctor), who authorised clozapine.

Clozapine was started on the 24 April 2023, under the "Off-Licence Agreement" with ZTAS (Zaponex Treatment Access System) monitoring company.

After the clozapine was started, there was a gradual improvement in the reported symptoms of schizophrenia and a gradual decline in the severity and frequency of incidents.

Unfortunately, the patient had Covid in May; and the Neutrophils decreased further. On the 26 May 2023, the Neutrophil count dropped to 1.4.

After discussing with the Medical Advisor at ZTAS, the BEN (benign ethnic neutropenia) criteria were used. It should be noted that the patient was a Caucasian and did not have BEN. The advice from ZTAS was for FBC monitoring twice a week.

9 June 2023: Further discussion with with the Medical Advisor who recommended,"I added the updated treatment plan to her notes. The cut-offs for RED are now WBC < 2.5, NC < 0.7 (so, 0.7 still would be seen as an amber)". Daily FBC monitoring was recommended.

The MDT considered Lithium to boost the neutrophil count; however, the patient declined, stating that she will not consider this, as this medication leads to 'swelling of legs'.

The dose of Epilim Chrono and the doses of haloperidol were decreased and later stopped, as these drugs might be contributing to the lowered neutrophils, as suggested by the Medical Advisor.

13 June 2023: A declining neutrophil count and the potential for further decrease in neutrophils prompted me to have a clinical discussion with the Medical Advisor, and this was further discussed with the Consultant Haematologist from the local general hospital.

14 June 2023: G-CSF (Granulocyte-Colony Stimulating Factor), 300 micrograms OD, S/C, was prescribed (Filgrastim) by the Consultant Haematologist.

- *The patient received the three doses on 14 June 2023, 15 June 2023 and 16 June 2023.*
- *She did not report any flu like symptoms or bony pain*
- *She was relatively stable in both her physical and mental health*

19–23 of June: Filgrastim 300 mcg was given three times a week for next week (19 June 2023, 21 June 2023 and 23 June 2023).

26 June 2023: The Consultant Haematologist advised Filgrastim 300 mcg three times a week for the next 2 weeks; and reflected that he will review FBC on 10 July 2023. The G-CSF was discussed with the medical adviser.

10 July 2023: The Consultant Haematologist advised that "If she goes down to two injections a week, a pre-dose FBC would be

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good (typically sampling in the morning before an evening dose of G-CSF)." From the week beginning on 10 July 2023, the dose of Filgrastim was reduced to twice a week, as the neutrophil count was maintained adequately, and the FBC remained within the normal limits.

Her overall mental state in June and July improved. The patient enjoyed the BBQ on 15 June 2023 in the Courtyard with her fellow peers. Her budgeting had improved. Her mood improved, and her quality of life improved. Due to her increased mobility with Section-17 leaves to the community, she lost 5.5 kgs. Her weight on 22 June 2023 was 159 kg, as compared to 165.5 kg on 23 April 2023 (Clozapine was started on 24 April 2023). Incidents had gradually started decreasing in intensity and frequency, and she was slowly recovering, although she still had residual positive symptoms of schizophrenia.

From the Week Beginning 21 August 2023, the Dose of Filgrastim Was Reduced to Once a Week

On 26 September 2023, the once-a-day S/C injection of G-CSF was stopped on the advice of the Consultant Haematologist as the FBC remains above the recommended normal levels. The monitoring frequency of FBC was continued every 2 weeks (2/52).

In the professional meeting on 10 October 2023, her progress, risks, and care pathway were re-discussed with representatives from her CMHT (community mental health team).

Step-down to the open rehabilitation unit was agreed, and she was discharged when a bed became available.

3 | Discussion

Clozapine is the gold standard evidence-based treatment of choice for treatment-resistant schizophrenia [1]. However, clozapine can induce serious, life-threatening adverse effects, including neutropenia and agranulocytosis. Most serious neutropenia leading to clozapine cessation occurs within 18 weeks of treatment and three-quarters by the end of the first year. Risk factors include patients with a lower baseline WBC at clozapine initiation, being Afro-Caribbean, and younger age. The risk is not dose-related [2].

The current guidelines in the UK mandate weekly FBC monitoring during the first 18 weeks and biweekly monitoring for the remainder of the year, followed by 4-weekly monitoring thereafter [2, 3].

Most serious neutropenia leading to clozapine cessation occurs within 18 weeks of treatment and becomes negligible after 2 years. The authors recommend that weekly haematological monitoring after the first 18 weeks could be safely reduced to once every 4 weeks and ceased after 2 years unless clinically indicated [4]. The mechanism of action of clozapine-induced neutropenia is unknown; it is thought to be related to the drug's effect on WBC precursors; both immune-mediated and direct cytotoxic effects are proposed; and this early drop in neutrophil count before 2 years is strongly tied to the clozapine drug's mechanisms or patient genetics and is not coincidental.

It is possible that clozapine is not the causative agent in some cases of coincidental neutropenia [5]. Ruling out other causes of coincidental neutropenia (e.g., COVID-19 infection or other viral/bacterial, benign ethnic neutropenia, other co-prescribed medications [antipsychotic medications, sodium valproate, proton pump inhibitors]) is important after 2 years of treatment with clozapine, as the risk of developing neutropenia drops significantly and becomes nonspecific to clozapine.

Although, the risk of neutropenia and agranulocytosis is highest in the first 3 months, this may occur at any time, even after years of treatment [6, 7]. Our patient had developed clozapine-associated neutropenia after 13.5 years.

After the red result in February 2021, various antipsychotic medications (risperidone, amisulpride, olanzapine, pericyazine and haloperidol) were tried sequentially and in combination; however, these were unsuccessful in reducing the patient's psychopathology. These were combined with other prescribed medications (mood stabilisers and medications for her agitated behaviours); however, these were not effective. The patient was very unwell, presenting with florid psychosis, and she continued presenting with risks to herself and others; the MDT found it difficult to manage her risks.

'Before restarting clozapine in a patient who has previously experienced neutropenia/agranulocytosis, an extensive risk/benefit analysis should be made. In this analysis, the likelihood that the first neutropenia/agranulocytosis was a true and typical clozapine-induced dyscrasia should be determined (This information was obtained from the factsheet from the ZTAS website, www.ztas.co.uk)'.

As there were apparently no clear other medical reasons to explain the blood dyscrasias, like co-prescribed medication, auto-immune diseases or vitamin deficiencies, amongst other conditions, the team looking after her in the community assumed that the neutropenia was clozapine-induced.

Despite trying to find out retrospectively what could have caused neutropenia, this was difficult, as this information was not available from the community mental health team or the community provider where the patient was residing. However, on hindsight, it is possible that the neutropenia in the community could be due to the COVID-19 pandemic, as the episodes of neutropenia (Amber results finally culminating in two red results) occurred between March 2020 and March 2021.

Patients who experience neutropenia with clozapine are at an increased risk of developing neutropenia on rechallenge. Hence, rechallenging a patient who previously experienced neutropenia with clozapine is a difficult clinical decision [8].

There is accumulating evidence to suggest that rechallenging with clozapine should be considered in most patients with clozapine-associated neutropenia (mild to moderate neutropenia) who do not respond to other treatments. A more careful risk–benefit analysis is needed in cases of clozapine-associated agranulocytosis (severe neutropenia). Success rates for rechallenge of up to 80% have been reported, and rechallenge should be considered in most patients [9].

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Clozapine rechallenges and initiation despite neutropenia—a practical, step-by-step guide has been produced [10].

In the USA, the Risk Evaluation and Mitigation Strategies (REMS) programme for clozapine (www.clozapinerems.com) eliminated WBC monitoring and updated the recommended ANC (absolute neutrophil count). The US Food and Drugs Administration (FDA) endorsed this change in October 2015 [11].

A recent paper in 2021 highlighted an urgent need for revising the UK clozapine monitoring guidelines to improve outcomes in treatment-resistant schizophrenia. The paper concluded that implementation of the updated US FDA's monitoring criteria in the United Kingdom would significantly reduce clozapine discontinuation due to haematological reasons [12]. Another study recommends that the ANC threshold of $\leq 1.0 \times 10^9$ per L could be used in more jurisdictions [4]. *However, in the UK, both ANC and WBC levels are mandatory and are monitored by the drug companies (In this case the ZTAS).*

In the context of clozapine treatment, most neutropenia that occurs after 2 years of treatment is coincidental to the use of clozapine. This paper highlights a need for greater awareness and earlier diagnosis of BEN (benign ethnic neutropenia), and opined that ruling out other causes of neutropenia is important in such cases [12].

Benign ethnic neutropenia (BEN) is the most common cause of chronic neutropenia seen in individuals of African, Middle Eastern and West Indian descent. This phenotype is broadly defined by an absolute neutrophil counts (ANC) below 1.8×10^9 cells/L in the absence of other causes, without an increased risk of infection [13].

Due to poor response to the ongoing antipsychotic treatment, after obtaining a second opinion from the NPU (National Psychosis Unit, London), clozapine was started. An authorisation from the SOAD (second opinion appointed doctor) was obtained. A SOAD is to safeguard people who do not, or cannot, agree to their treatment; and is required to make decisions, based on their own independent judgement, taking into consideration clinical rationale, the interests and preferences of the patient, the Mental Health Act 1983, the Mental Capacity Act 2005 and the Code of Practice.

After mandated clozapine cessation for suspected clozapine-induced neutropenia, clozapine rechallenge can be successful [14]. A meta-analysis from 2012 showed that re-challenge after neutropenia was successful in 69.6% of patients. After agranulocytosis, a rechallenge is only successful in 20% of patients [15].

Clozapine was started on 24 April 2023, under the 'Off-Licence Agreement' with ZTAS (Zaponex Treatment Access System) monitoring company. After clozapine was started, there was a gradual decline in the severity and frequency of incidents.

Unfortunately, the patient developed COVID-19 infection, which was confirmed by a blood test, in May, and the Neutrophils decreased further. On 26 May 2023, the Neutrophil count dropped to 1.4.

Neutropenia's are indeed often seen in combination with a COVID-19 infection or COVID-19 vaccination. South London and Maudsley (SLAM) NHS Trust had introduced a protocol during the Covid-19 pandemic to address such cases [16].

COVID-19 infections can cause a transient, mild reduction in absolute neutrophil counts (ANC) in patients taking clozapine, which is often viral-induced rather than true clozapine-induced agranulocytosis.

Distinguishing clozapine-associated neutropenia caused by a viral infection from true clozapine-induced neutropenia is critical to prevent unnecessary discontinuation of clozapine. The clinical guidance often recommends temporarily reducing the clozapine dose if fever or acute systemic infection occurs and closely monitoring blood counts rather than automatically stopping treatment unless severe neutropenia persists or is proven to be drug-induced [17]. This study highlights how localised acute infections and associated inflammatory cytokine responses can inhibit the CYP1A2 metabolic pathway, leading to dangerous drug accumulation.

After discussing with the Medical Advisor at ZTAS, a modified criteria like the BEN (benign ethnic neutropenia) were used as recommended by SLAM. It should be noted that the patient was a Caucasian and did not have BEN. FBC monitoring twice a week was recommended.

The relationship between clozapine and infection is indeed quite complex. Infection or inflammation may induce bioactivation of clozapine into its nitrenium ions, which can exert a toxic reaction that induces apoptosis and gives rise to elevated cytokine levels. Clozapine can also function as a hapten and induce an IgG, IgM or IgE-mediated hypersensitivity reaction [18].

Several reports have suggested that valproate may slightly increase serum clozapine levels and levels of clozapine metabolites, and as the patient was also taking valproate, this could have added to the toxicity. In such cases, it is a good practice to revisit patient-related variables that might have a bearing on serum clozapine levels, including drug-drug interactions [19].

Exploring the potential effect of polypharmacy on the haematologic profiles of clozapine patients is important, as certain non-psychiatric medications that are co-prescribed with clozapine like antibiotics, proton pump inhibitors, and autonomic agents are associated with an increased risk of adverse haematological reactions [20]. Haloperidol, procyclidine and diazepam were tapered and stopped in June. As Epilim chrono can potentially lead to a lower neutrophil count, this was reduced and stopped on 3 July 2023. These changes were made after discussing with the Medical Adviser from ZTAS.

In selected patients, cases of clozapine associated neutropenia can be managed with either Lithium or Colony-Granulocyte Stimulating Factor (C-GSF). These decisions should be made based on the patient's unique circumstances, after a thorough risk-benefit analysis, discussions with the stakeholders involved in the patient's care, and close monitoring is essential.

Off-label prescribing of Lithium medication can be used to treat clozapine induced neutropenia [21]; however, this may not be

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suitable for all patients. The mechanism of lithium-induced leucocytosis is unknown, and there is a risk that Lithium may mask the preliminary state of neutropenia, leading to a more severe agranulocytosis without warning [22].

The patient declined the offer of lithium; she stated that she will not consider this, as this medication leads to 'swelling of legs'.

On 9 June 2023, a declining neutrophil count and the potential for further decrease in neutrophils prompted me to have a clinical discussion with the Medical Advisor, and this was further discussed with the Consultant Haematologist from the local general hospital on 13 June 2023, to consider G-CSF, and the following plan was agreed. *The cut-offs for a RED result on FBC monitoring were set at WBC < 2.5, and Neutrophil Count < 0.7 (so, 0.7 still would be seen as an amber).* Daily FBC monitoring was recommended.

The patient was given Filgrastim [a Granulocyte-Colony Stimulating Factor (G-CSF)]. The G-CSF was given for a short period of time; this provided symptomatic treatment, and the patient was able to continue with clozapine treatment. G-CSF is a potent stimulator of the bone marrow, and this leads to the production of neutrophils and stem cells in the blood stream (i.e., supports haematopoietic cell production), thereby allowing clozapine to be continued or re-introduced.

A couple of systematic reviews on the use of G-CSF in clozapine rechallenge have been published [23, 24]. Most of the supporting data are derived from case reports and case series.

This article [23] reported that there were no clear clinical or laboratory predictors of successful rechallenge; however, initial neutropenia was more severe in successful cases compared to unsuccessful cases. Cases co-prescribed lithium had lower success rates of rechallenge (60%) compared to those who were not prescribed lithium (81%).

This article [24] reported that 75% of published cases remained on clozapine with the use of continual prophylactic G-CSF or after single G-CSF administrations. Seventy percent of patients in receipt of continual prophylactic G-CSF were successfully maintained on clozapine.

This article [24] also highlights that in true clozapine-related agranulocytosis, the G-CSF is not recommended.

Regular and prophylactic G-CSF could mask a developing clozapine-induced agranulocytosis due to bone marrow exhaustion. In such cases, there will not be any option to raise the neutrophil count if prophylactic G-CSF has been administered. Therefore, it is best to only consider using G-CSF as an add-on in response to clozapine-induced neutropenia or febrile neutropenia and not as a prophylactic measure [25].

In our patient, add-on filgrastim was prescribed, not regularly or prophylactically.

On 14 June 2023, G-CSF (Granulocyte-Colony Stimulating Factor), 300 μg OD, S/C, was prescribed (Filgrastim) by the Consultant Haematologist.

From the week beginning on 10 July 2023, the dose of Filgrastim was reduced to twice a week, as the neutrophil count was maintained adequately.

From the week beginning 21 August 2023, the dose of Filgrastim was reduced to once a week.

On 26 September 2023, the once-a-day S/C (subcutaneous) injection of G-CSF was stopped on the advice of the Consultant Haematologist as the FBC remains above the recommended normal levels.

The main adverse effects from long-term use of Filgrastim are musculoskeletal pain, capillary leak syndrome, severe splenomegaly, splenic rupture and serious pulmonary adverse events. Allergic reaction to Filgrastim and high cost are additional considerations.

As noted above in the case presentation, the patient gradually became better, the incidents reduced, the psychosis was manageable, her quality of life improved, and she was finally discharged in November 2023.

After her step-down from the open rehabilitation unit to the community, our patient continued with the clozapine, and there were no concerns with the FBC. Since being discharged from our low secure unit, the patient has not had any amber or red results on FBC. I obtained this information on 23 July 2025 from ZTAS.

4 | Conclusion

Clozapine is the gold standard, evidence-based treatment of choice for treatment-resistant schizophrenia. However, clozapine can induce the serious side-effect of neutropenia and agranulocytosis. Rechallenging a patient who previously experienced neutropenia with clozapine is a difficult clinical decision.

Ruling out other causes of coincidental neutropenia (e.g., COVID-19 infection or other viral/bacterial, benign ethnic neutropenia, other co-prescribed medications [antipsychotic medications, sodium valproate, proton pump inhibitors]) is important after 2 years of treatment with clozapine, as the risk of developing neutropenia drops significantly and becomes nonspecific to clozapine.

Currently, there is a lack of evidence for long-term regular or prophylactic use of Filgrastim for clozapine-induced neutropenia and agranulocytosis, as long-term regular or prophylactic use could mask a developing clozapine-induced agranulocytosis due to bone marrow exhaustion. In true clozapine-related agranulocytosis, the G-CSF is not recommended.

In selected patients, co-prescription with Filgrastim, a cytokine recombinant Granulocyte-Colony Stimulating Factor (G-CSF) for a short-term period, may provide symptomatic treatment when a patient develops neutropenia whilst taking clozapine and may allow continuation of clozapine. Most of the supporting data are derived from case reports and case series.

A risk-benefit discussion with the patient, the MDT (multidisciplinary team), involving the medical adviser from the clozapine monitoring service (In this case it was ZTAS) and the

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Consultant Haematologist from the local catchment area is advisable. An independent opinion was sought from the SOAD (second opinion appointed doctor), and the NPU (National Psychosis Unit), as these are recommended good practice. Also, the IMCA (Independent mental health advocate) was involved in professional's meeting to safeguard the patient's rights.

Author Contributions

Devender Singh Yadav: conceptualization, investigation, writing – original draft, methodology, writing – review and editing, data curation, project administration, resources.

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Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Material of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supporting File: pnp70019-sup-0001-Case_Report_July_2025_Additional_information.docx.

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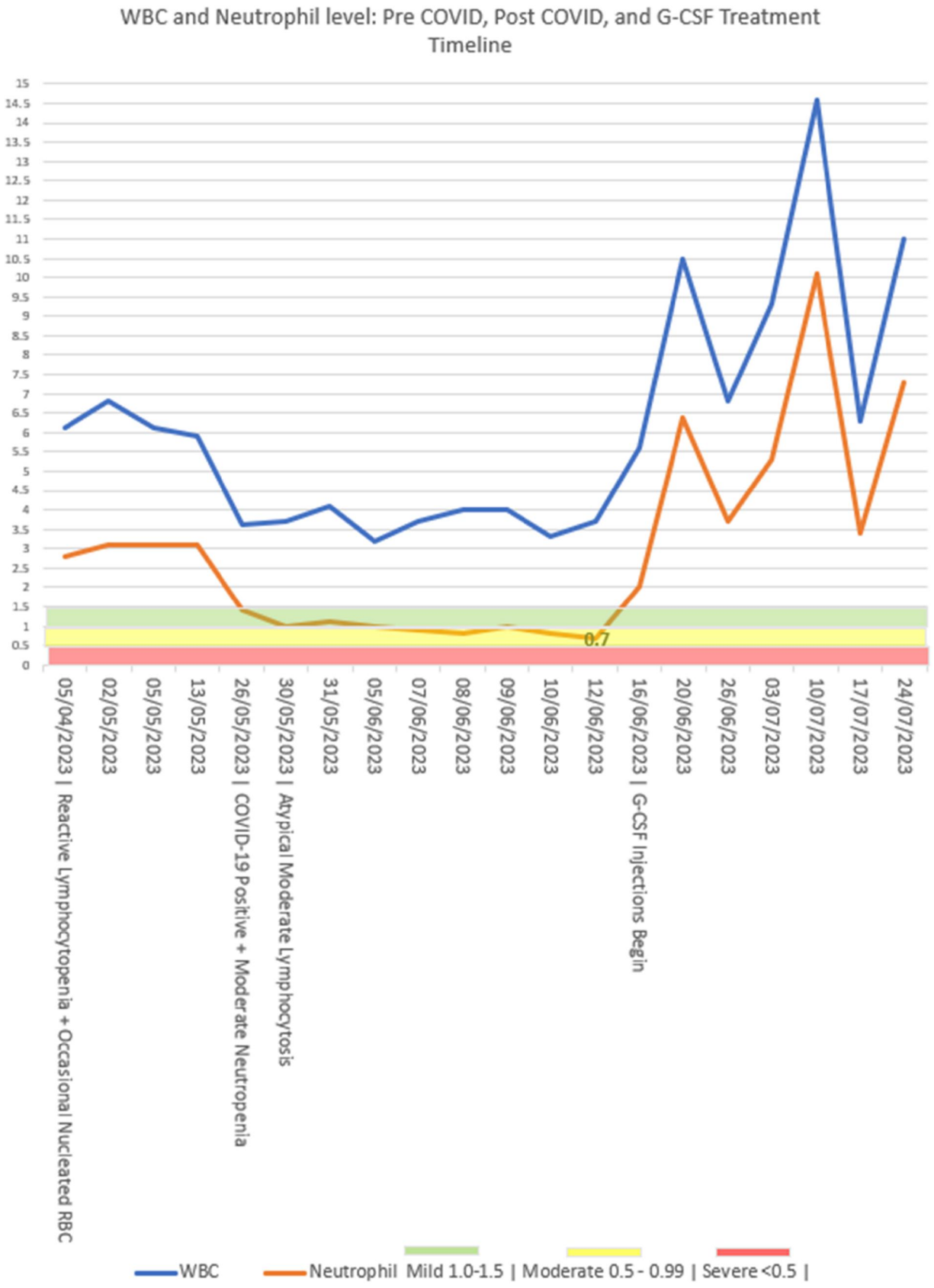
Appendix 1



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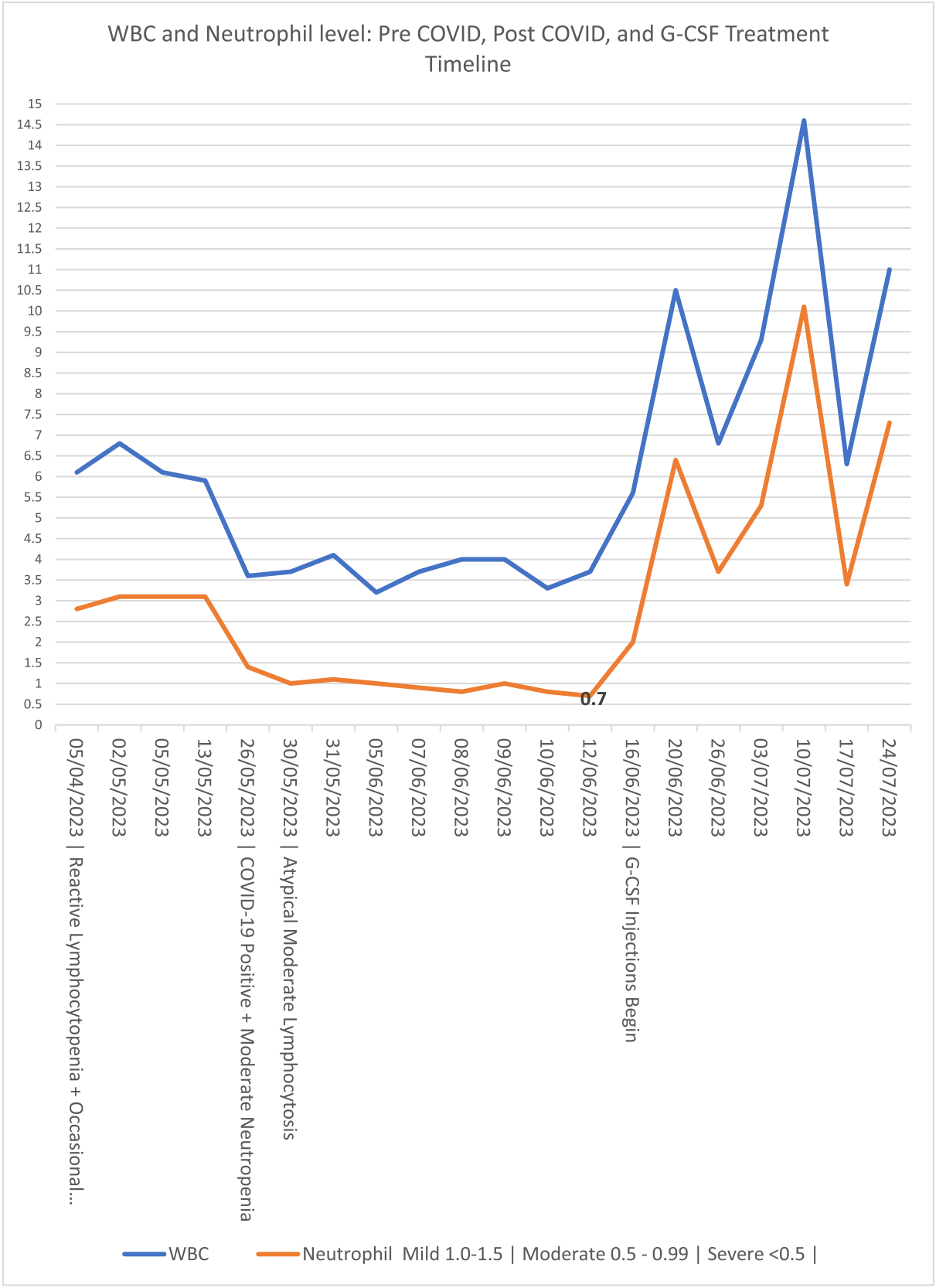

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Appendix 2

Classification and Causes of Neutropenia: The below table has been adapted from the clinical examples based on guidance from the MSD Manual Professional Edition and Clinical References (https://www.msdmanuals.com/professional/hematology/leukopenias/neutropenia#Etiology_v970590).

Classification of Neutropenia Severity:

- **Mild Neutropenia:** 1.0 to 1.5×10^9/L (1000–1500 cells/μL)—Lower risk of infection, often monitored or managed depending on the underlying cause.
- **Moderate Neutropenia:** 0.5 to 0.99×10^9/L (500–999 cells/μL)—Increased vulnerability to bacterial and viral infections.
- **Severe Neutropenia:** Less than 0.5×10^9/L (fewer than 500 cells/μL)—High risk of serious, potentially life-threatening infections requiring immediate medical attention. *(Some classifications also separate counts below 0.2×10^9/L as very severe or absolute absence as agranulocytosis).*

Causes of Neutropenia Table:

Category	Example	Possible mechanism	Relevant to this case
Medications and toxins	Chemotherapy and radiation therapy destroy bone marrow cells. Certain antibiotics, mood stabilisers (sodium valproate, carbamazepine), antipsychotics (Clozapine), proton-pump inhibitors, and thyroid drugs also lower counts.	Idiosyncratic or immune destruction, or direct bone marrow toxicity	Clozapine, sodium valproate, and haloperidol are relevant to this case
Infections	Viruses (Covid-19, HIV, CMV, EBV, influenza), severe bacterial sepsis, protozoal infections	Temporary bone marrow suppression, immune-mediated clearance, or increased tissue margination.	The patient tested positive for Covid-19 infection
		Bacterial sepsis and severe infections use up white blood cells faster than the body can make them.	
Autoimmune and immune	Systemic Lupus Erythematosus (SLE), Felty syndrome and Primary autoimmune neutropenia	Antineutrophil antibodies causing peripheral destruction.	The antineutrophil antibodies were negative in this case
		Conditions like lupus or rheumatoid arthritis cause the immune system to mistakenly attack and destroy neutrophils.	
Hypersplenism	Inflammatory conditions	Sequestration and pooling of white blood cells in an enlarged spleen. Hypersplenism traps white blood cells in the spleen, lowering the number circulating in the blood.	No evidence of hypersplenism was noted in this case
Nutritional deficiencies	Copper, Vitamin B6 or B12 deficiency	Ineffective haematopoiesis in the marrow due to impaired DNA synthesis	No evidence of Vitamin B6 or B12 deficiency noted in this case
Benign ethnic neutropenia (BEN)	Benign ethnic neutropenia is common in individuals of Middle Eastern, African or West Indian descent	Normal genetic polymorphism (e.g., DARC gene) resulting in lower baseline neutrophil counts without increased risk of infection	The patient was a Caucasian.
			BEN not relevant to this case.
Bone marrow infiltration by cancers or bone marrow failure	Lymphoma's, Leukaemia's, Metastatic solid tumours, Myelofibrosis.	Crowding or replacement of normal hematopoietic tissue in the bone marrow.	Not relevant to this case
	Bone marrow failure in Aplastic Anaemia.	Conditions like aplastic anaemia stop the body from making new blood cells.	
Inherited/congenital	Severe congenital neutropenia (Kostmann syndrome), cyclic neutropenia	Specific genetic mutations (e.g., *ELANE*, *HAX1*) causing arrest of myeloid cell maturation and apoptosis	Not relevant to this case

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