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Review Article

Hematopoietic Growth Factors in Idiosyncratic Drug-Induced Neutropenia: Mechanisms, Clinical Evidence, and Future Perspectives

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Abstract:

Background and aim: Idiosyncratic, non-chemotherapy drug-induced neutropenia and agranulocytosis are rare but potentially life-threatening adverse drug reactions, frequently affecting older or medically complex patients. Prompt recognition, immediate discontinuation of the causative agent, and supportive care are essential to minimise morbidity and mortality.

Methods: We conducted a narrative review of published literature, pharmacovigilance registries, and expert-consensus guidelines on the pathophysiology, clinical management, and therapeutic role of hematopoietic growth factors (HGFs) in idiosyncratic drug-induced neutropenia.

Results: HGFs — particularly granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) — accelerate neutrophil recovery, reduce infectious complications, and improve clinical outcomes. Observational data consistently support early administration in severe neutropenia (absolute neutrophil count [ANC] <0.5 × 109/L), although prospective randomised evidence is lacking.

Conclusion: HGFs are a cornerstone of management for idiosyncratic drug-induced agranulocytosis. Integration of pharmacogenomic risk stratification, next-generation growth factor therapeutics, digital health tools, and international registries offers a pathway toward more precise, patient-centred care.

Key words: hematopoietic growth factors; granulocyte colony-stimulating factor (g-csf); idiosyncratic neutropenia; agranulocytosis; drug-induced hematologic toxicity; gm-csf; supportive therapy; pharmacogenomics

1.Introduction

Idiosyncratic, non-chemotherapy-related drug-induced neutropenia and agranulocytosis are uncommon but potentially life-threatening adverse drug reactions (ADRs), most often defined by an absolute neutrophil count (ANC) <0.5 × 10^9/L. These syndromes carry a markedly increased risk of severe bacterial and fungal infections — particularly in elderly or immunocompromised patients — and can rapidly progress to sepsis if unrecognised [1, 2]. The underlying pathophysiology is thought to involve immune-mediated mechanisms, such as drug-dependent antibodies, or direct bone marrow toxicity. Establishing a definitive causal pathway is frequently challenging because of nonspecific clinical manifestations, variable latency between drug exposure and symptom onset, and overlap with other causes of neutropenia [3].

To date, more than 100 drugs spanning multiple therapeutic classes have been implicated, including antibiotics (β-lactams, sulfonamides), antithyroid agents (methimazole, propylthiouracil), antipsychotics (clozapine), and antiepileptics (carbamazepine) [1, 2, 4]. Limited clinical familiarity with these associations can result in delayed diagnosis and management, thereby increasing morbidity and mortality.

HGFs — particularly G-CSF — have been increasingly used in the treatment of severe idiosyncratic neutropenia. Observational cohorts and case series suggest that G-CSF accelerates neutrophil recovery, reduces hospital length of stay, and improves overall survival compared with supportive care alone [5–7]. However, robust prospective data are lacking; no large-scale trials have systematically addressed the optimal timing of initiation, dosing strategies, or criteria for patient selection in this context [1, 2].

This review synthesises current evidence on idiosyncratic drug-induced neutropenia and agranulocytosis, emphasising the role of HGFs in management. We discuss pathophysiological mechanisms, highlight high-risk pharmacological classes, examine clinical outcomes, and identify critical knowledge gaps, the resolution of which will be essential to optimise early recognition, risk stratification, and therapeutic interventions.

2. Epidemiology and Etiology

The annual incidence of severe non-chemotherapy drug-induced neutropenia or agranulocytosis is estimated at 1.6–15.4 cases per million population, with consistently higher rates observed among older adults and women [2, 8]. Although rare, this condition carries a hospital mortality of approximately 5–10%, highlighting its clinical significance and the critical need for prompt recognition [1, 2].

Among the most frequently implicated drugs are antithyroid agents — particularly methimazole and propylthiouracil — followed by psychotropic medications such as clozapine, levomepromazine, and carbamazepine. Antibiotics (notably β-lactams and trimethoprim-sulfamethoxazole) and antimalarials such as dapsone have also been repeatedly associated with idiosyncratic agranulocytosis [2, 8].

In contrast to chemotherapy-induced neutropenia, the risk is not dose-dependent, and onset may occur acutely within days or be delayed for several weeks following exposure [1, 2]. Populations at increased risk include elderly patients, individuals with renal impairment, and those receiving multiple concomitant hematotoxic drugs. Emerging evidence also implicates genetic susceptibility, including specific HLA haplotypes and pharmacogenomic variants that influence drug metabolism and immune responsiveness [10].

Insights from large-scale epidemiological registries — such as the Berlin Case-Control Surveillance Study and French pharmacovigilance databases — have been instrumental in identifying both high-risk medications and patient-specific susceptibility factors [11, 12]. Immediate withdrawal of the offending drug remains the cornerstone of management; supportive care including broad-spectrum antibiotics and G-CSF has been shown to accelerate neutrophil recovery and reduce morbidity [2, 7].

3. Mechanisms of Non-Chemotherapy Drug-Induced Neutropenia

The mechanisms underlying non-chemotherapy drug-induced neutropenia are heterogeneous and remain incompletely understood. Most cases are considered idiosyncratic, arising from either immune-mediated destruction of neutrophils or their progenitors, or from direct cytotoxic effects on hematopoietic precursors within the bone marrow [9].

According to the immune hypothesis, certain drugs or their reactive metabolites act as haptens, binding to neutrophil surface antigens or marrow-derived cells and eliciting an immune response [9, 13]. This may culminate in antineutrophil antibodies or activation of cytotoxic T cells, resulting in peripheral neutrophil destruction or marrow aplasia. Additional proposed mechanisms include oxidative stress and mitochondrial dysfunction induced by reactive metabolites (exemplified by dapsone and clozapine), as well as direct cytotoxic effects on early myeloid progenitors (notably with β-lactam antibiotics and sulfonamides) [9].

Genetic predisposition contributes further variability: polymorphisms in drug-metabolising enzymes (e.g., NAT2, CYP2D6) and specific HLA alleles modulate individual susceptibility. The latency period between drug exposure and onset of agranulocytosis is highly variable, reflecting these diverse pathways — from acute immunological reactions with rapid onset to cumulative marrow toxicity developing over weeks to months [14].

Bone marrow examination frequently demonstrates hypocellularity with granulocytic maturation arrest, although findings vary according to the offending agent and timing of biopsy [2]. This mechanistic heterogeneity underscores the importance of considering multiple pathways in clinical evaluation, and provides the rationale for HGF therapy, which stimulates early myeloid progenitors irrespective of the initiating insult [9, 14].

4. Clinical Manifestations and Diagnosis

The clinical presentation of idiosyncratic drug-induced severe neutropenia is largely dictated by the depth and duration of neutropenia and by the presence of secondary infections [1]. Common early symptoms include fever, pharyngitis, malaise, and mucosal ulcerations. In cases of profound neutropenia (ANC $<0.5 \times 10^9$/L), patients are at substantial risk of sepsis, pneumonia, and invasive fungal infections, which can evolve rapidly [2]. Notably, neutropenia itself is typically clinically silent; most patients become symptomatic only after infection onset.

Diagnosis requires a high index of suspicion, particularly in elderly individuals, those receiving multiple medications, or patients with comorbidities predisposing to infection. Laboratory evaluation generally reveals isolated neutropenia on complete blood count, with preserved erythroid and platelet lineages. Bone marrow examination is not mandatory but may be valuable to exclude alternative aetiologies such as aplastic anaemia, myelodysplastic syndromes, or marrow infiltration [1, 4].

A comprehensive medication history spanning at least the previous three months is essential [15]. Widely applied diagnostic criteria include: (1) ANC $<1.5 \times 10^9$/L; (2) a temporal association with drug exposure; (3) documented neutrophil recovery following withdrawal; and (4) exclusion of alternative explanations [1, 2]. In selected instances, drug rechallenge or detection of antineutrophil antibodies may provide supportive evidence, although these strategies are infrequently used due to ethical concerns and methodological limitations.

5. Management Principles and Prognostic Factors

The cornerstone of management remains early recognition, immediate cessation of the offending agent, and supportive care tailored to both the severity of neutropenia and the patient's clinical status. Hospital admission is generally recommended for patients with ANC $<0.5 \times 10^9$/L who present with fever or other signs of infection. Empirical broad-spectrum intravenous antibiotics should be initiated promptly, with coverage directed against Gram-negative bacilli and, when clinically indicated, methicillin-resistant *Staphylococcus aureus* [1, 8].

Daily monitoring of complete blood counts is advised until neutrophil recovery is documented. Concurrent investigations — including blood and urine cultures, chest imaging, and, when indicated, bronchoalveolar lavage — should identify the source of infection and guide targeted therapy [1, 8].

Ambulatory management may be appropriate for selected low-risk patients without fever or infection who have stable vital signs, reliable follow-up, and rapid access to hospital care [2]. Adjunctive G-CSF can accelerate neutrophil recovery in such settings, though prophylactic antibiotics are generally not indicated [8]. Most patients demonstrate recovery within one to three weeks of drug withdrawal; delayed recovery is more common in elderly patients and those with prolonged profound neutropenia.

Prognostic factors consistently associated with adverse outcomes include: age >65 years; profound neutropenia (ANC $<0.1 \times 10^9$/L); concomitant renal or hepatic dysfunction; and presentation with sepsis or shock [16]. HGFs — particularly G-CSF — may expedite recovery and improve outcomes, although the magnitude of benefit appears variable across patient populations [5, 16]. Overall hospital mortality for non-chemotherapy drug-induced agranulocytosis approximates 5–10%, but

can be substantially reduced by timely recognition, immediate drug withdrawal, and aggressive supportive management [2].

6. Special Considerations in High-Risk Populations

Elderly individuals represent a particularly vulnerable population because of age-related changes in haematopoiesis, frequent comorbidities, polypharmacy, and altered drug metabolism [1, 8]. Coexisting renal or hepatic impairment further amplifies susceptibility, prolongs neutropenia, and increases the likelihood of infectious complications; proactive monitoring and early intervention are therefore essential when initiating medications with known hematotoxic potential.

Patients with underlying autoimmune diseases receiving antithyroid agents are at elevated risk, reflecting both the immunogenic potential of these drugs and disease-related immune dysregulation [1, 2]. Psychotropic medications — clozapine in particular — warrant careful haematological surveillance during the first three months of therapy, when the incidence of severe neutropenia peaks.

Individuals with a history of drug-induced neutropenia, genetic polymorphisms affecting drug metabolism, or specific HLA haplotypes may exhibit heightened susceptibility [10, 14]. Pharmacogenomic and immunogenetic risk factors could facilitate personalised prescribing and preventive strategies, although routine genetic screening remains investigational.

Across all populations, permanent discontinuation of the offending drug and pharmacovigilance reporting are mandatory to prevent recurrence and inform public health safety. Tailoring monitoring protocols, optimising supportive care, and integrating emerging predictive tools — such as pharmacogenomic profiling and digital risk models — may further improve outcomes in these vulnerable groups.

7. Hematopoietic Growth Factors: Mechanism of Action and Pharmacology

HGFs — primarily G-CSF and GM-CSF — are pivotal cytokines that regulate the proliferation, differentiation, and functional activation of haematopoietic progenitor cells in the bone marrow [17]. G-CSF agents — including filgrastim, lenograstim, and the pegylated derivative pegfilgrastim — exert lineage-specific effects on neutrophils, accelerating maturation, enhancing mobilisation into peripheral circulation, and promoting functional competence (**Table 1**). In contrast, GM-CSF (sargramostim) has broader activity across myeloid lineages, including neutrophils, monocytes, eosinophils, and dendritic cells, and may provide additional immunomodulatory benefits [5, 17].

Both agents act through cognate receptors on haematopoietic progenitors, triggering JAK/STAT and PI3K/AKT intracellular signalling cascades that promote proliferation, differentiation, and survival. Pharmacokinetically, filgrastim is rapidly absorbed after subcutaneous administration with a half-life of 3–4 hours, whereas pegfilgrastim exhibits an extended half-life of 15–80 hours, permitting less frequent dosing. Standard regimens typically involve 5–10 µg/kg/day until ANC exceeds 1.5×10^9/L for at least 48 hours [5, 18].

The emergence of biosimilar G-CSFs has expanded accessibility, providing cost-effective alternatives with comparable efficacy and safety [18]. Adverse effects are generally mild, most commonly manifesting as bone pain, while rare but serious events include splenic rupture, leukocytosis, or hypersensitivity reactions [18].

Growth Factor	Type	Half-life	Common use	Side effects
Filgrastim	rHu G-CSF	3–4 h	Drug-induced neutropenia, oncology	Bone pain, leukocytosis
Lenograstim	Glycosylated G-CSF	~3–4 h	Similar to filgrastim	Similar to filgrastim
Pegfilgrastim	Pegylated G-CSF	15–80 h	Chemotherapy-induced neutropenia	Bone pain, rare ARDS
Sargramostim	GM-CSF	3–5 h	Neutropenia with monocytopenia; G-CSF failure	Fever, fluid retention

ARDS, acute respiratory distress syndrome; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; rHu, recombinant human.

Table 1: Key characteristics of hematopoietic growth factors.

8. Clinical Evidence Supporting Use Of G-Csf and Gm-Csf

Although randomised controlled trials are lacking — owing to the rarity and heterogeneity of idiosyncratic neutropenia — observational studies and case series consistently indicate that HGFs accelerate haematological recovery and reduce infection-related morbidity [2, 4, 5]. A large European retrospective study of 203 patients demonstrated that G-CSF therapy shortened the median duration of neutropenia from 10 to 6 days, decreased infectious complications, and reduced hospital length of stay compared with supportive care alone [19]. Similarly, a Spanish cohort reported that early G-CSF initiation improved outcomes, particularly in older patients and those with significant comorbidities [15] (**Table 2**).

Evidence emphasises the importance of prompt intervention — ideally within 48 hours of diagnosis — to optimise recovery. GM-CSF has shown efficacy in patients refractory to G-CSF or those with combined cytopenias, although comparative data between agents remain limited. Growth factor therapy does not appear to increase relapse rates or mortality, supporting a favourable risk–benefit profile in idiosyncratic agranulocytosis [5, 8].

Prognostic factor	Impact on outcome
Age >65 years	Poorer outcome
ANC <0.1 × 10^9/L	Higher mortality risk
Sepsis or shock at presentation	Increased complications
Renal failure	Poorer outcome

Prognostic factor	Impact on outcome
Delay in diagnosis or drug withdrawal	Prolonged recovery
Early G-CSF administration	**Improved/accelerated recovery**
Multiple comorbidities	Worse prognosis

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

Table 2. Prognostic factors in non-chemotherapy drug-induced agranulocytosis.

9. Comparative Pharmacology: Filgrastim, Lenograstim, Pegfilgrastim, and Sargramostim

Several G-CSF formulations are available for clinical use [17]. While mechanistically similar, they differ in pharmacokinetics, immunogenicity, and dosing schedules. Filgrastim (non-glycosylated recombinant human G-CSF) is commonly administered daily in Europe, whereas pegfilgrastim allows once-per-cycle dosing, though its use in non-chemotherapy settings remains limited [5, 17].

Lenograstim's glycosylation enhances receptor affinity and reduces clearance, potentially yielding faster neutrophil recovery. Pegfilgrastim's prolonged half-life is advantageous in oncology but may offer limited additional benefit in self-limiting idiosyncratic neutropenia, and is associated with higher cost [17]. Sargramostim (GM-CSF) exerts broader myeloid effects, useful for concurrent cytopenias or G-CSF-refractory cases, but is linked to higher rates of fever, arthralgia, and fluid retention. Consequently, G-CSF remains the preferred first-line agent for most patients, with selection guided by availability, comorbidities, and prior response [5, 17].

10. Safety, Limitations, And Controversies

HGFs are generally well tolerated. Bone pain is the most frequently reported adverse effect, occurring in up to one-third of treated individuals; although typically mild to moderate, it may necessitate symptomatic management with paracetamol or non-steroidal anti-inflammatory agents [5]. Rare but serious complications — including splenic rupture, leukocytosis, capillary leak syndrome, and acute respiratory distress syndrome — have been described, underscoring the need for vigilant clinical monitoring [1, 5].

A persistent limitation in this field is the absence of prospective, randomised controlled trials, reflecting the rarity, heterogeneity, and often-unpredictable onset of idiosyncratic drug-induced neutropenia [1, 8]. Therapeutic recommendations consequently rely heavily on retrospective cohorts, pharmacovigilance registries, and expert consensus. The wide diversity of implicated medications, along with variability in the depth and duration of neutropenia, complicates the development of standardised treatment algorithms [2].

Although early G-CSF administration is widely advocated in cases of profound neutropenia or established infection, its role in moderate or asymptomatic presentations remains debated, given that spontaneous recovery is common once the offending agent is withdrawn [2, 5]. Concerns regarding potential overuse of G-CSF, cost-effectiveness, and the risk of overtreatment also merit consideration [1]. The increasing availability of biosimilar G-CSF products introduces more affordable options, but their long-term safety in this off-label context requires continued pharmacovigilance.

Given these uncertainties, large-scale international registries and robust post-marketing surveillance systems remain essential to refine patient selection, clarify indications, and advance the safe and judicious use of HGFs in idiosyncratic drug-induced agranulocytosis [15].

11. Perspectives And Future Directions

Several emerging scientific and clinical avenues hold considerable promise for improving the prevention and management of non-chemotherapy drug-induced neutropenia.

11.1. Pharmacogenomic risk stratification

A major frontier lies in the integration of pharmacogenomic strategies to identify individuals at heightened susceptibility to idiosyncratic reactions [19]. The association between specific HLA alleles and clozapine-induced agranulocytosis provides a compelling proof of concept, demonstrating the potential for genotype-informed prescribing and individualised risk mitigation [20]. Extending genomic screening to other high-risk medications may enable earlier identification of vulnerable patients and help avert severe complications.

11.2. Next-generation hematopoietic growth factors

Novel formulations — including long-acting, engineered, or multispecific colony-stimulating factors — may offer enhanced pharmacodynamic profiles, reduced dosing frequency, and improved tolerability. Agents designed to target multiple myeloid lineages or to modulate inflammatory networks could benefit patients with refractory or complex cytopenias for whom current therapies remain suboptimal.

11.3. Digital health and artificial intelligence

Artificial intelligence and machine learning applied to large-scale electronic health record datasets may enable earlier detection of drug-induced neutropenia by identifying subtle trends in laboratory parameters, symptom trajectories, or prescribing patterns before overt clinical deterioration occurs [20]. Such tools could support proactive monitoring and decision-making, particularly in high-risk or polymedicated populations.

11.4. International registries and collaborative research

Strengthening collaborative research infrastructures is essential. International registries, harmonised pharmacovigilance systems, and multicentre observational studies are needed to generate robust epidemiological data, refine diagnostic and causality-assessment criteria, and inform standardised treatment algorithms. Close collaboration among haematologists, internists, clinical pharmacists, and regulatory agencies will be critical to improving the timely identification, reporting, and management of this uncommon yet serious ADR. Ultimately, integrating precision medicine paradigms into routine haematological practice may reshape both prevention and care for idiosyncratic agranulocytosis.

Key Points

1. **Clinical problem:** Idiosyncratic, non-chemotherapy drug-induced neutropenia and agranulocytosis are rare but life-threatening, often presenting with fever, mucosal lesions, or severe infections. Elderly patients and those with polypharmacy are at greatest risk.
2. **Mechanism:** Pathogenesis is heterogeneous, including immune-mediated neutrophil destruction, direct marrow toxicity, oxidative stress, and genetic predisposition (HLA alleles, drug-metabolising enzyme polymorphisms).

3. **Role of G-CSF:** Accelerates neutrophil maturation and mobilisation; reduces infection-related complications; daily filgrastim or long-acting pegfilgrastim formulations are available.
4. **Role of GM-CSF:** Broader myeloid stimulation; useful in combined cytopenia or G-CSF-refractory cases.
5. **Safety:** Generally well tolerated; the most common adverse effect is bone pain; rare complications include splenic rupture and leukocytosis.
6. **Clinical evidence:** Retrospective and observational studies consistently show faster neutrophil recovery, shorter hospitalisation, and lower morbidity with early HGF administration, particularly in severe neutropenia.
7. **Challenges:** Absence of prospective trials, heterogeneous patient populations, and uncertainty regarding use in moderate or asymptomatic presentations.
8. **Future directions:** Pharmacogenomic risk stratification; next-generation long-acting or multi-lineage HGFs; AI-driven early detection; international registries.
9. **Take-home message:** HGFs are a cornerstone of management for idiosyncratic drug-induced neutropenia; integration of personalised medicine approaches may further improve outcomes.

12. Conclusion

Idiosyncratic non-chemotherapy drug-induced neutropenia and agranulocytosis — although rare — remain clinically significant and potentially life-threatening ADRs, particularly in older adults and patients with multimorbidity. Early recognition, immediate discontinuation of the causative agent, and aggressive supportive care are central to optimising outcomes. HGFs — most notably G-CSF — have demonstrated consistent benefit in accelerating neutrophil recovery, reducing infectious complications, and improving clinical trajectories, with a generally favourable safety profile when applied judiciously.

Persistent challenges include the rarity and heterogeneity of the syndrome, the absence of randomised trials, and substantial variation in clinical presentation and management practices. Future advances will depend on the integration of pharmacogenomic risk stratification, development of novel growth factor therapeutics, incorporation of digital health and AI-driven early detection tools, and expansion of international registries to strengthen the evidence base.

Taken together, these strategies offer a pathway toward a more precise, mechanistically informed, and patient-centred approach to the prevention and treatment of idiosyncratic drug-induced neutropenia — with the potential to meaningfully improve safety, outcomes, and quality of care.

Disclosures

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