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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:

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 minimize morbidity and mortality. Hematopoietic growth factors (HGF), particularly granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF), have emerged as valuable therapeutic tools, accelerating neutrophil recovery, reducing infectious complications, and improving clinical outcomes. This review synthesizes current understanding of the pathophysiology, high-risk medications, and clinical presentation of idiosyncratic neutropenia, with an emphasis on HGF pharmacology, formulations, efficacy, and safety. Limitations of the existing evidence, including the lack of prospective trials and heterogeneity in drug exposure and patient populations, are discussed. Finally, we outline future directions, including pharmacogenomic risk stratification, next-generation growth factors, and digital health strategies, highlighting opportunities to optimize individualized patient care. Integrating mechanistic insights with emerging therapeutic approaches positions HGFs as a cornerstone of management and a focus for future research in this rare but serious condition.

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

Introduction

Idiosyncratic, non-chemotherapy-related drug-induced neutropenia and agranulocytosis are uncommon but potentially life-threatening adverse drug reactions, most often defined by an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L. These syndromes are associated with a markedly increased risk of severe bacterial and fungal infections, particularly in elderly or immunocompromised patients, and can rapidly progress to sepsis if unrecognized [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 due to the nonspecific clinical manifestations, variable latency between drug exposure and symptom onset, and overlap with other causes of neutropenia [3]. Diagnosis is further complicated by generalized symptoms, which may be subtle or overlooked, leading to frequent delays in recognition after the offending medication is initiated.

To date, more than 100 drugs spanning multiple therapeutic classes have been implicated. These include 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. Awareness of at-risk medications, careful monitoring and early recognition remain critical to improving outcomes.

Hematopoietic growth factors (HGFs), particularly granulocyte colony-stimulating factor (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. As a result, guideline recommendations remain largely based on retrospective analyses, expert consensus, and clinical judgment [1, 2].

This review synthesizes current evidence on idiosyncratic drug-induced neutropenia and agranulocytosis, emphasizing the role of HGFs in management. We discuss pathophysiological mechanisms, highlight high-risk pharmacological classes, examine clinical outcomes, and identify critical gaps in knowledge. Addressing these gaps through prospective studies and standardized reporting will be essential to optimize early recognition, risk stratification, and therapeutic interventions, ultimately improving patient care and reducing preventable complications.

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 substantial mortality risk of approximately 5–10% in hospitalized patients, 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, typically prescribed for autoimmune thyroid disorders, followed by psychotropic medications such as clozapine, levomepromazine, and carbamazepine [1, 2]. Additionally, antibiotics — notably β-lactams and trimethoprim-sulfamethoxazole — and antimalarials such as dapsone, have been repeatedly associated with idiosyncratic agranulocytosis [2, 8].

The pathogenesis is generally immune-mediated, involving drug-dependent antibodies, or arises from direct cytotoxic effects on granulocytic precursors in the bone marrow [9]. In contrast to chemotherapy-induced neutropenia, the risk is not dose-dependent, and onset may occur rapidly 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]. In clinical practice, immediate withdrawal of the offending drug remains the cornerstone of management. Supportive care, including broad-spectrum antibiotics and administration of G-CSF, has been shown to accelerate neutrophil recovery and reduce morbidity, underscoring the importance of timely intervention [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 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 process may culminate in the generation of 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, as exemplified by dapsone and clozapine. Direct cytotoxic effects on early myeloid progenitors have also been described, particularly with β-lactam antibiotics and sulfonamides [9]. Genetic predisposition contributes further variability, with polymorphisms in drug-metabolizing enzymes (e.g., NAT2, CYP2D6) and specific HLA alleles modulating individual susceptibility.

The latency period between drug exposure and onset of non-chemotherapy drug-induced agranulocytosis is highly variable, reflecting the diverse underlying pathways — from acute immunologic 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 may vary according to the offending agent and timing of biopsy [2]. Immune-mediated cases typically manifest as an abrupt neutrophil decline within hours to days, whereas toxic or idiosyncratic mechanisms often present more insidiously.

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]. Recognition of these diverse mechanisms also informs risk stratification, drug monitoring, and individualized therapeutic strategies in affected patients.

4. Clinical Manifestations and Diagnosis

The clinical presentation of idiosyncratic drug-induced severe neutropenia is often nonspecific and largely dictated by both the depth and duration of neutropenia, as well as by the presence of secondary infections [1]. Common early symptoms include fever, pharyngitis, malaise, and mucosal ulcerations, which may be subtle and easily overlooked. In cases of profound neutropenia (ANC $<0.5 \times 10^9$/L), patients are at substantial risk of developing life-threatening complications, including sepsis, pneumonia, and invasive fungal infections. These complications can evolve rapidly, highlighting the critical importance of early recognition and intervention [2]. Notably, neutropenia itself is typically clinically silent; most patients only become symptomatic after the onset of infection.

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

A comprehensive medication history spanning at least the previous three months is essential, as the latency between drug exposure and neutropenia onset can vary, particularly with long acting or depot formulations [15]. Exclusion of infectious, autoimmune, and hematologic causes remains a critical step. Immediate discontinuation of the suspected drug is the cornerstone of management.

Widely applied diagnostic criteria for drug-induced neutropenia include: (1) ANC $<1.5 \times 10^9$/L, (2) a temporal association with drug exposure, [3] documented neutrophil recovery following withdrawal of the offending

agent, and [4] exclusion of alternative explanations. 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 [1, 2]. Early recognition and diagnosis are pivotal to mitigating morbidity and preventing potentially fatal infectious complications.

5. Management Principles and Prognostic Factors

The cornerstone of management for non-chemotherapy drug-induced severe neutropenia or agranulocytosis 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 × 10^9/L who present with fever or other signs of infection. In such cases, 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]. Multidisciplinary discussion regarding the use of HGFs, particularly G-CSF, is often warranted in these high-risk settings.

Daily monitoring of complete blood counts is advised until neutrophil recovery is documented. Concurrent investigations—including blood and urine cultures, chest imaging (radiography or computed tomography), and, when indicated, lumbar puncture or bronchoscopy—should be performed to identify the source of infection and guide targeted therapy [1, 8]. Protective isolation measures may be considered, although their efficacy outside oncology remains debated. In afebrile, clinically stable patients, outpatient management under strict monitoring may be feasible [1]. Most patients demonstrate neutrophil recovery within 1–3 weeks after drug withdrawal; delayed recovery is more frequently observed in elderly patients, those with comorbidities, or individuals with prolonged profound neutropenia.

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. Outpatient care necessitates frequent blood count monitoring, patient education regarding infection signs, and prompt hospitalization if fever or other complications arise [2]. Adjunctive G-CSF can accelerate neutrophil recovery, supporting ambulatory management in appropriate cases, though prophylactic antibiotics are generally not indicated [8]. Permanent discontinuation of the implicated drug and formal pharmacovigilance reporting remain mandatory.

Several prognostic factors have been consistently associated with adverse outcomes, including age >65 years, profound neutropenia (ANC <0.1 × 10^9/L), concomitant renal or hepatic dysfunction, and presentation with sepsis or shock (16). The interval to neutrophil recovery is a key determinant of prognosis. HGFs, particularly G-CSF, may expedite recovery and improve outcomes; however, the magnitude of benefit appears variable across patient populations (5, 16). Overall, non-chemotherapy drug-induced agranulocytosis carries a hospital mortality rate of approximately 5–10%, but timely recognition, immediate drug withdrawal, and aggressive supportive management can substantially reduce this risk [2].

6. Special Considerations in High-Risk Populations

Certain patient groups are at increased risk of developing severe non-chemotherapy drug-induced neutropenia or experiencing complications thereof. Elderly individuals represent a particularly vulnerable population due to age-related changes in hematopoiesis, frequent comorbidities, polypharmacy, and altered drug metabolism [1, 8]. The coexistence of renal or hepatic impairment further amplifies susceptibility, prolongs neutropenia, and increases the likelihood of infectious complications. In this context, proactive monitoring and early intervention are essential, particularly when initiating medications with known hematotoxic potential.

Patients with underlying autoimmune diseases, such as Graves' disease receiving antithyroid agents, are also at elevated risk, reflecting both the immunogenic potential of the drugs and disease-related immune dysregulation [1, 2]. Psychotropic medications, including clozapine and other atypical antipsychotics, warrant careful hematologic surveillance, especially during the first three months of therapy when the incidence of severe neutropenia peaks. Regular complete blood count monitoring and patient education regarding infection signs are integral components of safe therapy in these populations.

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

Outpatient management of low-risk patients may be feasible with structured follow-up, frequent laboratory monitoring, and rapid access to hospital care if infection develops [2, 8]. High-risk patients, however, require inpatient management, aggressive infection surveillance, and consideration of early G-CSF therapy to accelerate neutrophil recovery. Across all populations, permanent discontinuation of the offending drug and pharmacovigilance reporting are mandatory to prevent recurrence and inform public health safety.

Collectively, these considerations underscore the importance of individualized risk assessment and highlight the need for heightened vigilance in populations prone to severe non-chemotherapy drug-induced neutropenia or agranulocytosis. Tailoring monitoring protocols, optimizing 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, particularly G-CSF and granulocyte macrophage colony-stimulating factor (GM-CSF), are pivotal cytokines that regulate the proliferation, differentiation, and functional activation of hematopoietic 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 mobilization into the peripheral circulation, and promoting functional competence (Table 1). In contrast, GM-CSF (e.g., sargramostim) has broader activity across myeloid lineages, including neutrophils, monocytes, eosinophils, and dendritic cells, and may provide additional immunomodulatory benefits [5, 17].

Growth Factor	Type	Target Lineage	Half-life	Common Use Cases	Side Effects
Filgrastim	rHu G-CSF	Neutrophils	3–4 hours	Drug-induced neutropenia, oncology	Bone pain, leukocytosis
Lenograstim	Glycosylated G-CSF	Neutrophils	~3–4 hours	Similar to filgrastim	Similar to filgrastim
Pegfilgrastim	Pegylated G-CSF	Neutrophils	15–80 hours	Chemotherapy-induced neutropenia	Bone pain, rare ARDS
Sargramostim	GM-CSF	Neutrophils, monocytes	3–5 hours	Neutropenia with monocytopenia, G-CSF failure	Fever, fluid retention

Table 1: Key Characteristics of Hematopoietic Growth Factors.

Both G-CSF and GM-CSF act through binding to cognate receptors on hematopoietic progenitors, triggering intracellular signaling cascades such as JAK/STAT and PI3K/AKT pathways, thereby promoting proliferation, differentiation, and survival. Pharmacokinetically, filgrastim is rapidly absorbed after subcutaneous administration, with a half-life of 3–4 hours, whereas pegfilgrastim, due to pegylation, exhibits an extended half-life of 15–80 hours, permitting less frequent dosing. Standard regimens for neutropenic patients typically involve 5–10 µg/kg/day until the absolute neutrophil count (ANC) exceeds 1.5×10^9/L for at least 48 hours [5, 18]. GM-CSF is less commonly employed in Europe but may be considered in patients with concomitant monocytopenia or in those unresponsive to G-CSF.

The emergence of biosimilar G-CSFs has expanded accessibility, providing cost-effective alternatives with comparable efficacy and safety [18]. While these agents are primarily indicated for oncology-related neutropenia, off-label use in idiosyncratic, non-chemotherapy drug-induced neutropenia is increasingly reported, supported by retrospective analyses and expert consensus [5]. Adverse effects are generally mild, most commonly manifesting as bone pain, while rare but serious events include splenic rupture, leukocytosis, or hypersensitivity reactions [18].

8. Clinical Evidence Supporting Use of G-CSF and GM-CSF

Although randomized controlled trials are lacking due to the rarity and heterogeneity of idiosyncratic neutropenia, observational studies and case series consistently indicate that HGFs accelerate hematologic recovery and reduce infection-related morbidity [2, 4, 5]. A large European retrospective study involving 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 emphasizes the importance of prompt intervention, ideally within 48 hours of diagnosis, to optimize recovery. GM-CSF has shown efficacy in patients refractory to G-CSF or those with combined cytopenias, although comparative data between agents remain limited. Importantly, growth factor therapy does not appear to increase relapse rates or mortality, supporting a favorable risk–benefit profile in idiosyncratic agranulocytosis [5, 8].

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

Several G-CSF formulations are available for clinical use, including filgrastim (non-glycosylated recombinant human G-CSF), lenograstim (glycosylated form), and pegfilgrastim (pegylated long-acting derivative) (17). While mechanistically similar, these agents differ in pharmacokinetics, immunogenicity, and dosing schedules. Filgrastim 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, yet their use in non-chemotherapy drug-induced neutropenia warrants careful consideration. 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 acetaminophen or non-steroidal anti-inflammatory agents (5). Other common adverse reactions include headache, local injection-site erythema, and fatigue. Rare but serious complications — including splenic rupture, leukocytosis, capillary leak syndrome, and acute respiratory distress syndrome (ARDS) — have been described, underscoring the need for vigilant clinical monitoring in hospitalized patients [1,5].

A persistent limitation in this field is the absence of prospective, randomized controlled trials, a reflection of the rarity, heterogeneity, and often-unpredictable onset of idiosyncratic drug-induced neutropenia [1, 8]. Consequently, current therapeutic recommendations 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 standardized, evidence-based 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, particularly given that spontaneous recovery is common once the offending agent is withdrawn [2,5].

Concerns have also emerged regarding potential overuse of G-CSF in scenarios where conservative management might be equally effective, raising questions about cost-effectiveness, resource allocation, and the risk of overtreatment [1]. Ethical challenges arise in situations of uncertain drug causality — for example, in multimorbid or polymedicated patients — in whom growth factor initiation may be considered despite diagnostic ambiguity. The increasing availability of biosimilar G-CSF products introduces more affordable options, but their long-term safety and performance in this off-label context require continued pharmacovigilance and systematic evaluation.

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. 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 individualized risk mitigation [20]. Extending genomic screening to other high-risk medications may enable earlier identification of vulnerable patients and help avert severe complications.

Parallel advances in the development of next-generation HGFs are also noteworthy. 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.

Beyond pharmacologic innovation, digital health technologies provide an additional opportunity to transform clinical practice. 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.

Finally, strengthening collaborative research infrastructures is essential. International registries, harmonized pharmacovigilance systems, and multicenter observational studies are needed to generate robust epidemiological data, refine diagnostic and causality assessment criteria, and inform standardized treatment algorithms. Close collaboration among hematologists, internists, clinical pharmacists, and regulatory agencies will be critical to improving the timely identification, reporting, and management of this uncommon yet serious adverse drug reaction. Ultimately, integrating precision medicine paradigms into routine hematologic practice may reshape both prevention and care for idiosyncratic agranulocytosis.

12. Conclusion

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

Persistent challenges include the rarity and heterogeneity of the syndrome, the absence of randomized 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-centered approach to the prevention and treatment of idiosyncratic drug-induced neutropenia — with the potential to meaningfully improve safety, outcomes, and quality of care.

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