



State of Art Antithyroid Drug-Induced Neutropenia and Agranulocytosis

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Abstract

Antithyroid Drugs (ATDs) - principally carbimazole, methimazole (thiamazole), and propylthiouracil - remain central to the treatment of hyperthyroidism but can rarely cause idiosyncratic neutropenia and agranulocytosis, a potentially fatal adverse drug reaction. Agranulocytosis is conventionally defined by an absolute neutrophil count below $0.5 \times 10^9/L$ and may develop abruptly after a previously normal blood count. This Seminar reviews contemporary epidemiology, drug- and patient-related risk factors, mechanisms, pharmacogenomic susceptibility, clinical presentation, differential diagnosis, monitoring, and management. Risk is heterogeneous and reflects ATD exposure, dose, age, population, and genetic background. HLA-B*38:02 and HLA-DRB1*08:03 are strongly associated with susceptibility in several Asian populations, whereas HLA-B*27:05 is particularly relevant in European cohorts; these associations are not yet sufficient to support universal pre-treatment screening. Fever, sore throat, or other infectious symptoms during ATD treatment should prompt immediate blood-cell assessment, and confirmed or strongly suspected agranulocytosis requires immediate withdrawal of the culprit drug. Febrile profound neutropenia is a medical emergency requiring prompt empirical antimicrobial therapy. G-CSF can accelerate neutrophil recovery in selected patients, although an independent mortality benefit remains unproven. After true ATD-induced agranulocytosis, re-exposure should be avoided and definitive treatment with radioiodine or thyroidectomy should be considered. Prevention therefore rests primarily on patient education and rapid symptom-triggered testing, with selective periodic monitoring where local circumstances justify it. Prospective validation of population-specific pharmacogenomic and clinical risk models is now needed to determine whether earlier detection or genotype-guided treatment improves patient-important outcomes.

Keywords: Antithyroid Drugs; Carbimazole; Methimazole; Propylthiouracil; Neutropenia; Agranulocytosis; Graves' Disease; Pharmacogenomics; G-CSF; Pharmacovigilance

Introduction

Synthetic Antithyroid Drugs (ATDs), principally Carbimazole (CBZ), Methimazole (MMI; thiamazole), and Propylthiouracil (PTU), have been used for more than 70 years and remain a major component of the medical treatment of hyperthyroidism, particularly Graves' disease. They may be used as definitive medical therapy or to restore euthyroidism before radioactive iodine or thyroid surgery [1, 2]. Carbimazole is a prodrug that is rapidly converted to methimazole, whereas PTU is administered as the active thionamide. ATDs inhibit thyroid peroxidase-mediated oxidation and organification of iodide and the subsequent coupling of iodotyrosine residues within thyroglobulin, thereby reducing thyroid hormone synthesis. PTU additionally inhibits type 1 deiodinase-mediated peripheral conversion of thyroxine (T₄) to triiodothyronine (T₃), an effect that may be clinically useful in selected patients with severe thyrotoxicosis [1, 2]. Experimental studies have also suggested immunomodulatory effects of thionamides, including effects on lymphocyte and immunoglobulin responses; however, the extent to which these effects are direct and clinically independent of restoration of euthyroidism remains uncertain [1-4].

Among the clinically important adverse effects of ATDs, idiosyncratic hematological toxicity is uncommon but potentially life-threatening. The most severe manifestation is agranulocytosis,

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Received Date: 10 Sep 2026

Accepted Date: 09 Oct 2026

Published Date: 10 Oct 2026

Citation:

Andrès E, Jannot X, Terrade J-E, Serraj K, Lorenzo-Villalba N. State of Art Antithyroid Drug-Induced Neutropenia and Agranulocytosis. WebLog J Thyroid Res. wjtr.2026.j1002. <https://doi.org/10.5281/zenodo.23336387>

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conventionally defined as an absolute neutrophil count (ANC) below $0.5 \times 10^9/L$ ($500/mm^3$), whereas neutropenia encompasses a broader spectrum of reductions in circulating neutrophils. For clinical purposes, neutropenia may be categorized as mild (ANC 1.0 - $1.5 \times 10^9/L$), moderate (0.5 - $1.0 \times 10^9/L$), or severe ($<0.5 \times 10^9/L$) [4-6].

ATD-induced agranulocytosis is generally considered an idiosyncratic adverse drug reaction, although both immune-mediated mechanisms and direct toxic effects on granulopoietic cells have been proposed. Immunological evidence includes drug-dependent neutrophil antibodies and cellular responses, whereas pharmacological and experimental data support the possibility of reactive metabolites and direct injury to myeloid precursors [5-7]. The clinical course can be abrupt: in the largest Japanese series, 84.5% of cases developed within 90 days of initiating ATD treatment, and more than half of patients with available recent blood counts had had a normal granulocyte count shortly before the event [7]. Consequently, a previously normal blood count does not reliably exclude subsequent abrupt agranulocytosis [6-8].

The reported incidence of ATD-induced agranulocytosis is approximately 0.1-0.5%, although estimates vary according to the population studied, the ATD used, the definition applied and the intensity of pharmacovigilance [6, 7, 9]. In a 30-year Japanese analysis of 754 cases, the estimated incidence among patients receiving ATDs was approximately 0.1-0.15% [7], whereas other large observational cohorts have reported somewhat higher rates. A recent meta-analysis has further revisited the relationship between ATD dose and agranulocytosis risk, suggesting that the historical concept of a completely dose-independent reaction may require qualification, particularly for methimazole [10]. Nevertheless, dose alone remains insufficient to predict individual susceptibility, and abrupt severe events can occur despite apparently appropriate dosing [5, 11-13].

The epidemiology of ATD-induced agranulocytosis is heterogeneous across populations and treatment settings. Much of the earlier pharmacogenetic and epidemiological literature originated from East Asian populations, particularly Taiwan, Japan and China, and involved predominantly methimazole or thiamazole. Treatment patterns differ substantially across Europe: methimazole is the preferred thionamide in many countries, whereas carbimazole is widely used in France and the United Kingdom because of its conversion to methimazole; PTU is generally reserved for specific clinical circumstances, particularly selected situations during pregnancy or when other thionamides cannot be used [2]. Accordingly, data derived from predominantly methimazole-treated Asian cohorts cannot automatically be extrapolated to European patients receiving carbimazole or PTU [11, 14, 15].

One of the major advances since earlier reviews has been the demonstration of a strong genetic contribution to susceptibility to ATD-induced agranulocytosis. In Taiwanese patients with Graves' disease, HLA-B*38:02 and HLA-DRB1*08:03 were identified as major susceptibility alleles, with particularly high risk among individuals carrying both alleles [16]. These findings were subsequently supported by studies in other East Asian populations. In Japanese patients, HLA-DRB1*08:03:02 was replicated as a susceptibility allele, while HLA-B*39:01:01 was identified as an additional susceptibility allele in a Japanese cohort [17]. A meta-analysis of pharmacogenomic studies confirmed significant associations between ATD-induced agranulocytosis and HLA-B*27:05, HLA-B*38:02 and HLA-DRB1*08:03, particularly for carbimazole/methimazole-associated

agranulocytosis [11, 18-20].

Importantly, pharmacogenomic susceptibility is not identical across ethnic groups. A genome-wide association study specifically conducted in a European population identified HLA-B*27:05 as the principal HLA signal associated with ATD-induced agranulocytosis [21]. This European-specific evidence is particularly relevant to clinical practice in France and other Western European countries and highlights the limitations of applying risk estimates derived exclusively from Asian populations. The genetic architecture of ATD-induced agranulocytosis therefore appears to be population-dependent, with several HLA alleles contributing to susceptibility rather than a single universal pharmacogenetic marker [15].

More recent work is beginning to distinguish the genetic determinants of severe agranulocytosis from those of less profound ATD-associated neutropenia. A 2026 pharmacogenomic study in Southern Han Chinese patients reported strong associations of HLA-B*38:02 and HLA-DRB1*08:03 with agranulocytosis but not with less severe ATD-induced neutropenia, supporting the possibility that these phenotypes have partly distinct biological determinants [22]. The same study proposed a multivariant predictive model with promising internal discrimination. Such findings are important conceptually, but their clinical implementation remains premature: the predictive value, calibration and cost-effectiveness of pre-treatment HLA screening need to be established prospectively and in the populations in which testing would be implemented [23].

Management recommendations have also evolved. Current European and American guidelines emphasize that patients receiving ATDs should be informed specifically about symptoms suggestive of agranulocytosis, particularly fever and sore throat, and should undergo an urgent differential white-cell count when such symptoms occur [1, 2]. Routine serial blood-count monitoring remains controversial because agranulocytosis may develop abruptly after a previously normal count and because the effectiveness of scheduled surveillance in preventing clinically significant events has not been consistently demonstrated [7, 14]. Once agranulocytosis is suspected or confirmed, the causative ATD should be discontinued immediately, appropriate microbiological assessment and empirical broad-spectrum antimicrobial therapy should be initiated in febrile or clinically infected patients, and Granulocyte Colony Stimulating Factor (G-CSF) may be considered in selected severe cases [6, 24]. Definitive treatment of the underlying hyperthyroidism, usually with radioactive iodine or thyroidectomy, is subsequently required because re-exposure to the causative thionamide is generally contraindicated after true agranulocytosis [2, 3, 5, 6, 17].

The aim of this review is therefore to provide a critical and clinically oriented update on ATD-induced neutropenia and agranulocytosis. We focus on what has changed since previous reviews, including contemporary epidemiological data, differences between carbimazole, methimazole/thiamazole and PTU, the distinction between neutropenia and true agranulocytosis, advances in the understanding of immune and pharmacogenomic mechanisms, and the emerging possibility of genotype-informed risk stratification. Particular attention is given to European evidence and its applicability to clinical practice in France. Finally, we integrate these data into a practical management framework addressing prevention, early recognition, diagnostic confirmation, immediate treatment, use of G-CSF, and subsequent definitive management of hyperthyroidism.

Epidemiology and Relative Risk

ATDs are an important cause of non-chemotherapy drug-induced neutropenia and agranulocytosis. Across pharmacovigilance and case-control series, ATDs consistently rank among the drugs associated with the highest relative risk of agranulocytosis, although their population-attributable fraction varies substantially according to the study design, background drug exposure, age distribution, and geographic prescribing patterns [8, 11-13]. The absolute risk nevertheless remains low, generally estimated at approximately 0.1-0.5% among patients receiving thionamides [5, 6, 8-10].

One of the largest historical cohorts was reported by Tajiri and Noguchi, who retrospectively evaluated 30,798 patients with Graves' disease treated with ATDs between January 1975 and December 2001. Among these patients, 109 developed ATD-induced agranulocytosis, corresponding to an overall incidence of 0.35% [21]. This cohort also provided important information regarding the potential benefit of G-CSF, with shorter recovery times after its introduction, although the observational design precluded definitive conclusions regarding causality or mortality benefit. Importantly, the frequently quoted incidence estimates of approximately 0.35% for methimazole and 0.37% for propylthiouracil derive from earlier Japanese data and should not be interpreted as evidence of equivalent risk in all populations or treatment regimens [17, 21, 22].

A second major Japanese cohort, conducted at Ito Hospital between 1983 and 2002 and including 50,385 patients with Graves' disease, identified 55 cases of ATD-related hematopoietic toxicity, including 50 cases of agranulocytosis and five cases of pancytopenia [14]. The median interval between initiation of ATD treatment and agranulocytosis was 69 days (range, 11-233 days). These data reinforce the marked clustering of events during the first weeks to months of therapy, while also demonstrating that clinically important hematological toxicity can occur later. This distinction is relevant when counselling patients because the risk cannot be considered completely restricted to the initial treatment period [16].

The largest dedicated analysis of ATD-induced agranulocytosis remains the Japanese series reported by Nakamura *et al.*, comprising 754 cases collected over approximately 30 years [8]. Agranulocytosis occurred within 90 days of treatment initiation in 84.5% of patients. The mean age at onset was 43.4 ± 15.2 years, and the female-to-male ratio was 6.3:1. Approximately 45% of patients were in their 40s or 50s. Compared with untreated patients with Graves' disease, affected patients were older and more frequently female. However, these findings should be interpreted in the context of the underlying epidemiology of Graves' disease and treatment exposure rather than as evidence of a strong sex-specific biological susceptibility. Importantly, among 211 patients with more than one granulocyte measurement before agranulocytosis, 62% had a normal granulocyte count within the preceding two weeks, illustrating the abrupt nature of the reaction in a substantial proportion of patients [8, 11].

The relative risk associated with ATD exposure is considerably greater than the absolute incidence might suggest. In the International Agranulocytosis and Aplastic Anemia Study, which included patients from seven European countries and Israel, ATD exposure was associated with a relative risk of 102 (95% CI, 38-275) for agranulocytosis, with an estimated excess risk of 6.3 cases per million users per week [24]. Similarly, a population-based Dutch study reported a relative risk of approximately 115 (95% CI, 90.5-

218.6) for agranulocytosis among ATD users [12]. These estimates emphasize that ATDs are among the strongest medication-associated risk factors for agranulocytosis, despite the low absolute frequency of the adverse reaction [9, 10].

The apparent incidence varies considerably between studies. Differences reflect not only the definition of agranulocytosis but also the intensity of case ascertainment, treatment dose, duration of exposure, ethnic background, and healthcare setting. Historical estimates of 0.2-0.5% are therefore best regarded as approximate ranges rather than universal incidence rates [6, 8]. More recent large-scale observational data suggest that the risk may be lower in some contemporary treatment settings, particularly with lower-dose methimazole regimens, although direct comparison across cohorts remains difficult because of substantial methodological heterogeneity [5, 11, 13].

The relationship between ATD dose and agranulocytosis is also more complex than previously assumed. Earlier observations suggested a dose-related increase in the risk of methimazole-associated agranulocytosis, whereas PTU appeared less clearly dose dependent. Recent pharmacovigilance and meta-analytic evidences have renewed interest in a possible dose-risk relationship, particularly for methimazole, but dose alone remains an insufficient predictor of individual susceptibility. Severe agranulocytosis may occur at conventional doses, and genetic, immunological and patient-specific factors probably contribute substantially to the observed heterogeneity [13, 14].

Geographical differences are particularly relevant when interpreting epidemiological data. Much of the largest evidence base originates from Japan, Taiwan and China, where methimazole or thiamazole has been widely used and where specific HLA susceptibility alleles are relatively frequent. European cohorts are smaller, but genetic studies indicate a partly distinct pharmacogenomic architecture, including an association between HLA-B*27:05 and ATD-induced agranulocytosis in European populations [25]. Consequently, incidence estimates and individual risk derived from East Asian cohorts should not be directly extrapolated to European populations, particularly in countries where carbimazole is commonly prescribed [15, 19].

Data from European clinical practice remains important. In a French single-center reference cohort, Andrès *et al.*, described 30 cases of severe neutropenia or agranulocytosis associated with ATDs, providing complementary information on clinical presentation, management, infectious complications and hematological recovery in a European population [18]. Such cohorts are particularly valuable because they reflect contemporary management within European healthcare systems and complement the much larger Japanese pharmacovigilance experience [25].

Mortality has clearly decreased compared with the early historical experience, largely as a consequence of earlier recognition, prompt withdrawal of the offending drug, rapid identification and treatment of infection, improved antimicrobial therapy and supportive hematological management. However, the precise contemporary case-fatality rate varies between series and should not be reduced to a universal threshold of <2%. In the 754-case Japanese series, 30 deaths were reported, corresponding to approximately 4% of cases, and several fatal outcomes were considered potentially preventable because of delays in recognition or treatment [8]. This observation

underscores a central epidemiological and clinical point: although ATD-induced agranulocytosis is uncommon, its prognosis is strongly influenced by the speed with which the drug is discontinued and infectious complications are recognized and treated [11, 25].

Overall, ATD-induced agranulocytosis should therefore be regarded as a rare but high-impact adverse drug reaction. Its absolute incidence is generally in the range of 0.1-0.5%, whereas its relative risk compared with the background population is markedly elevated. Most cases occur during the first three months of exposure, but delayed cases are well documented. Age, treatment dose, underlying disease, geographical and genetic background, and potentially HLA genotype may modify susceptibility, but no single clinical parameter currently identifies all patients at risk. These epidemiological characteristics provide the rationale for intensive patient education, rapid symptom-triggered blood-count assessment and continued investigation of pharmacogenomic strategies for individualized risk prediction.

Role of the Antithyroid Drug: Are All Molecules Equivalent?

Epidemiological and pharmacovigilance data suggest that the risk of neutropenia and agranulocytosis may differ between ATD molecules. However, direct comparisons are difficult because Carbimazole (CBZ), Methimazole (MMI; thiamazole), and Propylthiouracil (PTU) have been prescribed at different doses, in different populations and for different clinical indications. Differences in treatment duration, background incidence of agranulocytosis, reporting practices and genetic susceptibility further complicate comparisons. Consequently, the available evidence does not support a simple ranking of ATDs according to an intrinsic, universally applicable agranulocytosis risk.

Historical Japanese data illustrate this difficulty. In the large series reported by Tajiri and Noguchi, 93 of 109 cases of ATD-induced agranulocytosis occurred during methimazole treatment and 16 during PTU treatment. The corresponding reported incidences were approximately 0.35% and 0.37%, respectively [8]. These findings suggest broadly comparable absolute risks in that particular treatment setting, but they should not be extrapolated directly to contemporary low-dose treatment strategies or to populations in which the relative use of individual ATDs differs substantially [11, 17].

Other observational studies have suggested differences between molecules. Trotter reported a higher frequency of agranulocytosis with PTU than with carbimazole, approximately 0.7% versus 0.3% [21]. In the United Kingdom, analysis of national pharmacovigilance data collected between 1963 and 2003 identified substantially more reports associated with carbimazole than with PTU; however, these absolute numbers largely reflected the much greater use of carbimazole in routine clinical practice and therefore cannot be interpreted as comparative risks [22]. Similarly, analysis of the French Pharmacovigilance Database identified cases associated with both carbimazole and PTU and suggested a higher relative frequency of severe neutropenia with PTU [14, 22]. Such spontaneous-reporting data are valuable for signal detection but are inherently unsuitable for calculating incidence unless reliable denominators of drug exposure are available [14, 21, 22].

Carbimazole and methimazole should also be considered together when interpreting most pharmacological and pharmacogenomic data. Carbimazole is rapidly converted to methimazole and therefore represents a prodrug rather than a pharmacologically

independent thionamide. Consequently, observations described as “methimazole-associated” in the literature may have direct relevance to patients receiving carbimazole, particularly in European countries where carbimazole is widely prescribed. PTU, in contrast, is a distinct thionamide with additional inhibition of peripheral type 1 deiodination of thyroxine to triiodothyronine [1, 2].

The latency between ATD initiation and agranulocytosis is generally short, regardless of the molecule involved. In the International Agranulocytosis and Aplastic Anemia Study, approximately 82% of ATD-associated cases occurred within the first three months of exposure [7]. In a large Japanese series, 84.5% of cases developed within 90 days [8]. Earlier pharmacovigilance analyses reported median latencies of approximately 41 days for carbimazole and 36 days for PTU, while other pooled analyses have reported mean latencies in the range of 36-42 days for PTU, carbimazole and methimazole [4, 24]. These observations support particular vigilance during the first weeks and months of treatment, although late-onset agranulocytosis remains possible [9, 11, 21].

The relationship between ATD dose and agranulocytosis is particularly important because it may differ between molecules. A seminal case-control analysis by Cooper et al. reported an approximately 8.6-fold higher relative risk of methimazole-associated agranulocytosis among patients receiving doses greater than 40 mg/day compared with lower doses (95% CI, 1.7-44.1) [15]. This observation provided some of the strongest early clinical evidence for a dose-dependent component of methimazole-associated agranulocytosis. Subsequent studies have supported an association between higher methimazole doses and hematological toxicity, although the magnitude of the dose effect has varied between populations and studies [14].

The apparent dose dependence does not imply that agranulocytosis is a predictable, purely pharmacological toxicity. Cases can occur at conventional or relatively low doses, indicating that individual susceptibility remains a major determinant. Genetic predisposition, particularly HLA-associated susceptibility, may interact with drug exposure and other biological factors to determine whether treatment results in transient neutropenia, severe neutropenia or full agranulocytosis. Thus, dose should be regarded as a modifiable component of risk rather than as a sufficient predictor of toxicity.

Recent evidence has further strengthened the concept of a dose-risk relationship, particularly for methimazole, while also suggesting that the magnitude of this relationship may be smaller at contemporary lower doses than that observed in older high-dose treatment cohorts [13]. This distinction is clinically relevant because historical studies frequently involved substantially higher initial doses than those currently recommended for many patients with Graves' disease. The reduction in starting and maintenance doses achieved through modern titration strategies may therefore contribute to a lower absolute risk of severe hematological toxicity, although this hypothesis is difficult to establish independently from changes in case ascertainment and clinical management [13].

Current European and American guidelines consequently recommend using the lowest effective thionamide dose required to control hyperthyroidism and reducing the dose once biochemical control has been achieved [1, 2]. For methimazole/carbimazole, dose minimization is particularly relevant because higher exposure has been associated with a greater risk of adverse effects, including

Table 1: Risk factors and predisposing conditions for ATD-induced neutropenia and agranulocytosis.

Risk factor / condition	Evidence and comments
Age ≥40 years	~6× higher RR vs. younger patients; median onset 41-54 years across series [21, 24]
Female sex	6:1–10.4:1 female-to-male ratio; reflects hyperthyroidism epidemiology [20, 21]
Methimazole dose ≥40 mg/day	R ~8.6 (95% CI: 1.7-44.1); dose-dependence not established for PTU [24]
Underlying autoimmune disease	Positive rheumatoid factor; Sjögren's syndrome; SLE - limited data [25]
HLA-B*38:02 + HLA-DRB1*08:03	OR 48.41 (95% CI: 21.66-108.22) when both alleles present - Han Chinese GWAS [28]
HLA-B*27:05 (European)	OR 7.3 (95% CI: 3.81-13.96) - first European GWAS [29]
NOX3 rare variants (European)	Rare NOX3 variants were reported in a small European study; findings remain exploratory.
Cross-reactivity between ATDs	Cross-reactive adverse reactions have been reported, but no reliable rate for recurrent agranulocytosis has been established.

ATD: Antithyroid Drug; GWAS: Genome-Wide Association Study; HLA: Human Leukocyte Antigen; OR: Odds Ratio; PTU: Propylthiouracil; RR: Relative Risk; SLE: Systemic Lupus Erythematosus

agranulocytosis. PTU is not considered a safer alternative solely on the basis of hematological toxicity; its use is generally restricted to specific clinical circumstances because of its hepatotoxicity and other safety considerations [1-3].

Importantly, the available evidence does not establish that switching from one thionamide to another after uncomplicated neutropenia necessarily eliminates hematological risk. More importantly, after confirmed ATD-induced agranulocytosis, re-exposure to the causative thionamide should generally be avoided because recurrence may be rapid and potentially more severe. Cross-reactivity between thionamides has also been described, making substitution with another ATD an inappropriate strategy in patients with unequivocal previous agranulocytosis [5, 6, 19, 26].

Taken together, the evidence indicates that ATDs cannot be considered completely equivalent with respect to hematological toxicity, but neither can they be placed in a simple hierarchy of risk. Methimazole/carbimazole-associated agranulocytosis is supported by substantial evidence for a relationship with dose, whereas comparable dose dependence has been less consistently demonstrated for PTU. At the same time, PTU carries other major safety liabilities, particularly severe hepatotoxicity. The clinically relevant determinant is therefore the interaction between molecule, dose, duration of exposure, patient characteristics and genetic susceptibility. In contemporary practice, rational dose selection, avoidance of unnecessarily high thionamide exposure and early recognition of symptoms remain more clinically actionable than attempting to identify a universally “safer” ATD molecule.

The Patient Phenotype: Risk Factors and Genetic Susceptibility

Several patient-level, disease-related and treatment-related characteristics have been associated with an increased risk of ATD-induced neutropenia or agranulocytosis (Table 1). However, most established clinical risk factors have modest predictive value when considered individually. The identification of genetic susceptibility loci has therefore become an important focus of contemporary research, with increasing evidence that the genetic architecture of ATD-induced agranulocytosis differs between populations.

Demographic and Clinical Risk Factors

Age is one of the most consistently reported clinical risk factors. Across published series, the median age at onset generally ranges from approximately 40 to 55 years, and patients older than 40 years appear to be at greater risk than younger individuals [12, 13,

18, 20]. In the classical case-control study by Cooper et al., patients aged over 40 years had an approximately sixfold higher relative risk of methimazole-associated agranulocytosis than younger patients [20]. The Japanese experience similarly indicates that ATD-induced agranulocytosis is predominantly a disorder of adults rather than children or adolescents [8]. The biological basis of this age effect remains incompletely understood and may reflect age-related changes in immune responses, drug handling, comorbidity and treatment exposure rather than a single mechanistic pathway [11-14].

A marked female predominance has been reported in most series, with female-to-male ratios ranging from approximately 6:1 to 10:1 [18, 25]. This distribution largely parallels the strong female predominance of Graves' disease, the principal indication for ATD treatment. Nevertheless, an underlying sex-specific contribution to susceptibility cannot be completely excluded. Because most studies are based on patients with Graves' disease rather than on ATD-exposed populations with comparable numbers of men and women, it remains difficult to determine whether female sex independently increases the biological risk of agranulocytosis [13, 24].

The severity of the underlying thyrotoxicosis does not appear to provide a reliable predictor of subsequent agranulocytosis. Similarly, baseline leukocyte or neutrophil counts cannot reliably exclude future toxicity. Indeed, abrupt agranulocytosis may occur in patients whose previous blood counts were entirely normal [8]. This observation is clinically important because it limits the value of a single baseline complete blood count as a predictive tool [11].

Some studies have suggested an association between ATD-induced agranulocytosis and other autoimmune or immunological disorders, including rheumatoid arthritis, Sjögren syndrome and systemic lupus erythematosus, as well as the presence of rheumatoid factor [23]. These observations are biologically plausible given the proposed immune-mediated component of ATD-associated neutropenia, but the evidence remains inconsistent and is largely derived from relatively small or selected cohorts. Autoimmune comorbidity should therefore be regarded as a possible susceptibility marker rather than an established independent risk factor [20].

Other potential clinical modifiers, including previous exposure to ATDs, concomitant medications, ethnicity and the presence of pre-existing mild neutropenia, have also been investigated. However, none currently provides sufficient discrimination to allow reliable prediction of individual risk in routine practice. The clinical phenotype should consequently be interpreted as a composite of demographic, pharmacological, immunological and genetic characteristics rather

than as a simple risk score based on one or two variables.

Pharmacogenomic Susceptibility: What Is New?

The most important advance in the understanding of ATD-induced agranulocytosis has been the demonstration of strong pharmacogenomic associations, particularly involving the Human Leukocyte Antigen (HLA) region. These findings provide compelling evidence that at least a substantial proportion of cases represent genetically determined idiosyncratic drug reactions rather than unpredictable toxicity occurring independently of host biology.

A landmark genome-wide association study conducted in Taiwanese patients with Graves' disease identified two major susceptibility alleles, HLA-B*38:02 and HLA-DRB1*08:03 [28]. These associations were particularly strong in patients carrying both risk alleles, for whom the reported odds ratio for ATD-induced agranulocytosis reached 48.41 (95% CI, 21.66-108.22). The magnitude of these associations suggested that HLA genotyping might eventually permit prospective identification of a subset of patients at particularly high risk [18, 29].

Subsequent studies have replicated these associations in other East Asian populations. In northern Han Chinese patients, HLA-B*27:05, HLA-B*38:02 and HLA-DRB1*08:03 were associated with ATD-induced agranulocytosis [29]. Japanese studies subsequently confirmed the importance of HLA-DRB1*08:03 and identified HLA-B*39:01:01 as an additional susceptibility allele [26]. A systematic review and meta-analysis of pharmacogenomic studies further confirmed significant associations for HLA-B*27:05, HLA-B*38:02 and HLA-DRB1*08:03, although the magnitude of the association varied according to ethnicity, ATD molecule and study population [19, 20, 28, 30].

Importantly, the pharmacogenomic architecture is not uniform across ethnic groups. Hallberg *et al.*, performed the first large genome-wide association study specifically addressing ATD-induced agranulocytosis in a European population and identified HLA-B*27:05 as the principal HLA signal, with an odds ratio of approximately 7.3 compared with population controls [31]. The association was even stronger when cases were compared with hyperthyroid controls, emphasizing the importance of using an appropriate disease-exposed comparator. This European signal differs from the dominant HLA-B*38:02/HLA-DRB1*08:03 pattern observed in several East Asian populations [15].

Rare non-HLA variants may also contribute to susceptibility. Plantinga *et al.* reported rare variants affecting NADPH oxidase-related pathways, including NOX3, in patients of European ancestry [32]. Although these findings remain exploratory and require independent replication, they support a polygenic model in which several biological pathways may influence susceptibility to ATD-induced granulopoietic injury [27].

More recent pharmacogenomic studies have begun to address an important unresolved question: whether the genetic determinants of profound agranulocytosis are the same as those of less severe ATD-associated neutropenia. A 2026 study in Southern Han Chinese patients reported strong associations of HLA-B*38:02 and HLA-DRB1*08:03 with agranulocytosis, but not with less severe neutropenia. A multivariant model combining HLA and additional genetic markers showed promising discrimination in that population, with

an internally derived area under the receiver-operating-characteristic curve of approximately 0.91 [33]. These results are intriguing because they suggest that agranulocytosis and milder neutropenia may represent partially distinct pharmacogenomic phenotypes. However, the findings remain population-specific and require prospective external validation before clinical implementation [23].

The clinical utility of pre-treatment HLA screening therefore remains unresolved. A pharmacogenomic test would be most useful if it combined high sensitivity, clinically meaningful positive predictive value and sufficient population coverage while remaining cost-effective. This is challenging because ATD-induced agranulocytosis is rare: even a genetic marker with a high relative risk may have a limited positive predictive value when applied to a low-incidence population. Conversely, a negative test may substantially reduce risk for carriers of specific alleles without eliminating the possibility of disease caused by other genetic mechanisms.

The current evidence consequently supports a model of population-dependent pharmacogenomic susceptibility, rather than a single universal genetic test. In East Asian populations, HLA-B*38:02 and HLA-DRB1*08:03 appear particularly important, whereas HLA-B*27:05 has greater relevance in European cohorts. HLA-B*39:01:01 and additional non-HLA variants may further refine risk. Whether these findings should translate into routine pre-treatment screening will depend on prospective validation, allele frequency, test performance, treatment alternatives and local health-economic considerations.

Cross-Reactivity Between Antithyroid Drugs

Cross-reactivity between thionamides is clinically important but should not be confused with a precisely quantified risk of recurrent agranulocytosis. Carbimazole and methimazole are pharmacologically closely related because carbimazole is rapidly converted to methimazole. PTU is chemically distinct, yet cross-reactive adverse reactions between PTU and methimazole/carbimazole have been reported, particularly for cutaneous and other hypersensitivity reactions [5, 6, 19, 26].

Older reports suggested that approximately 15% of patients who developed an adverse reaction to one thionamide experienced a similar adverse reaction after exposure to another thionamide [22, 30]. However, this figure refers to adverse reactions overall and should not be presented as a specific recurrence rate for agranulocytosis. The frequency of true cross-reactive agranulocytosis is considerably less certain because of the rarity of the event and the limited size of published series [26].

The clinical implications are nevertheless clear. After confirmed ATD-induced agranulocytosis, re-exposure to the offending drug should be avoided. Switching to another thionamide is generally discouraged because of the potential for cross-reactivity and, more importantly, because alternative definitive treatments for Graves' disease are available [1, 2, 6]. This principle is particularly important after severe agranulocytosis, in which recurrence may occur rapidly and may be life-threatening [2, 3, 5].

In contrast, a history of a minor, non-hematological adverse effect does not automatically preclude the use of another ATD. Management should therefore distinguish between benign intolerance, hypersensitivity reactions, mild transient neutropenia and unequivocal agranulocytosis. This distinction is essential because

the risk–benefit balance of changing thionamides differs substantially according to the nature and severity of the initial adverse reaction.

Overall, the patient phenotype associated with ATD-induced agranulocytosis is best understood as the result of an interaction between age, disease characteristics, drug exposure, immune phenotype and genetic susceptibility. Clinical factors alone remain insufficiently discriminative, whereas HLA associations provide a biologically compelling basis for individualized risk stratification. The next step is therefore not simply to identify “high-risk patients,” but to determine whether integrated clinical and pharmacogenomic models can prospectively identify patients in whom the expected benefit of ATD treatment is outweighed by the risk of severe hematological toxicity.

Clinical Manifestations

The clinical spectrum of ATD-associated hematological toxicity ranges from transient mild neutropenia to profound agranulocytosis complicated by life-threatening bacterial or fungal infection. The distinction between these phenotypes is clinically important because their prognosis, management and relationship to ATD exposure may differ substantially.

Mild neutropenia, generally defined as an ANC of $1.0\text{--}1.5 \times 10^9/\text{L}$, may occur during ATD treatment and is frequently asymptomatic. Moderate neutropenia corresponds to an ANC of $0.5\text{--}1.0 \times 10^9/\text{L}$, whereas severe neutropenia is usually defined as an ANC below $0.5 \times 10^9/\text{L}$. Agranulocytosis is conventionally defined by an ANC $<0.5 \times 10^9/\text{L}$; an ANC $<0.1 \times 10^9/\text{L}$ identifies a particularly profound phenotype. Fever and infection are clinical manifestations, not components of the hematological definition [5, 6]. Importantly, fever, pharyngitis or infection are clinical manifestations of neutropenia and should not be incorporated into its hematological definition [4, 5].

Mild or moderate neutropenia detected during ATD treatment requires clinical reassessment rather than automatic attribution to the drug. Alternative causes, including viral infection, sepsis, autoimmune neutropenia, nutritional deficiencies, concomitant medications and underlying hematological disorders, should be considered. A repeat complete blood count with differential is appropriate when the abnormality is mild and the patient is clinically well. Whether ATD treatment should be continued, temporarily interrupted or discontinued depends on the ANC, its trajectory, the presence of symptoms, the indication for ATD therapy and the likelihood of an alternative cause. In contrast, a rapidly declining neutrophil count or an ANC approaching or below $0.5 \times 10^9/\text{L}$ should prompt immediate discontinuation of the suspected ATD and urgent clinical assessment [1–3, 5, 6].

The clinical presentation changes markedly with severe neutropenia or agranulocytosis. [Profound depletion of circulating neutrophils compromises host defense against bacterial and, in prolonged cases, fungal pathogens. Fever is the most characteristic presenting symptom and may be the only initial manifestation. Other frequent manifestations include odynophagia, sore throat, tonsillitis, pharyngitis, oral ulceration, gingivitis, skin or soft-tissue infection, pneumonia, urinary infection and anorectal infection. In severe cases, bacteremia, sepsis and septic shock may develop rapidly [3–6].

In a French pharmacovigilance series comprising 203 cases of ATD-associated severe neutropenia, the principal clinical

presentations included fever of unknown origin (26.3%), septicemia (13.9%), documented pneumonia (13.4%), acute tonsillitis or pharyngitis (9.3%), and septic shock (6.7%) [3]. These data illustrate the heterogeneous clinical spectrum and the predominance of infectious presentations. They should, however, not be interpreted as representative of the incidence of individual complications among all patients receiving ATDs because pharmacovigilance cohorts are enriched for clinically significant and hospitalized cases [25].

The risk of infection increases substantially as the ANC falls, particularly when the ANC is $<0.5 \times 10^9/\text{L}$ and especially when it approaches $<0.1 \times 10^9/\text{L}$ or when neutropenia is prolonged. The anatomical sites most commonly affected are the oropharynx, lungs, skin and anorectal region. Mucosal lesions may be prominent because the absence of neutrophils impairs the inflammatory response and local tissue defense. Consequently, severe infections may initially present with relatively limited local inflammatory findings despite extensive tissue involvement.

An important diagnostic characteristic of ATD-induced agranulocytosis is the potential dissociation between the severity of neutropenia and the apparent clinical examination. A patient may have profound agranulocytosis with little more than fever, malaise or odynophagia at presentation. Conversely, classical signs of bacterial inflammation may be attenuated because neutrophils are severely depleted. This phenomenon is particularly relevant to oropharyngeal and pulmonary infections and should lower the threshold for microbiological investigation and empirical antimicrobial treatment in febrile patients with severe neutropenia.

The timing of clinical manifestations is also important. Most ATD-induced agranulocytosis occurs during the first weeks to months after treatment initiation, but the reaction may occur after prolonged exposure [8]. Patients should therefore remain aware of warning symptoms throughout ATD treatment rather than only during the initial treatment period. Current guidelines specifically emphasize education regarding fever, sore throat and other symptoms suggestive of infection, with an urgent differential white-cell count when such symptoms occur [1, 2, 11, 25].

The presence of fever in a patient receiving an ATD should consequently be treated as a potential medical emergency until severe neutropenia has been excluded. A complete blood count with differential should be obtained without delay, together with appropriate clinical and microbiological assessment. If agranulocytosis is confirmed, the ATD should be stopped immediately and should not be restarted. In a febrile or clinically infected patient, empirical broad-spectrum antimicrobial therapy should be initiated according to the severity of illness, local resistance patterns and institutional protocols [1–6].

Empirical antibiotic administration before confirmation of neutropenia may modify the subsequent clinical phenotype. Oropharyngeal inflammation, focal infection and other local manifestations may become less conspicuous after antimicrobial exposure, leaving fever as the principal observable sign [4, 16]. This phenomenon reinforces the importance of obtaining a blood count promptly rather than relying exclusively on the physical examination to identify ATD-induced agranulocytosis [4, 6].

Severe ATD-induced agranulocytosis should therefore be considered a clinical syndrome rather than an isolated laboratory abnormality. Its recognition requires integration of the neutrophil

count, temporal relationship with ATD exposure, symptoms of infection and evaluation for alternative causes of neutropenia. Early identification is particularly important because the transition from an apparently uncomplicated febrile illness to bacteremia or septic shock can be rapid. The combination of patient education, prompt symptom-triggered blood-count assessment and immediate withdrawal of the causative ATD remains the cornerstone of prevention of adverse outcomes.

Differential Diagnosis

Severe neutropenia, generally defined as an ANC $\leq 0.5 \times 10^9/L$, has a broad differential diagnosis. In adults, medications represent one of the most frequent identifiable causes of severe neutropenia, particularly in hospitalized and pharmacovigilance populations [31, 32]. However, the presence of ATD exposure should not automatically establish causality. A systematic differential diagnosis is required, particularly because several disorders associated with autoimmune thyroid disease may themselves cause neutropenia [30, 31].

The first step is to confirm the abnormality by repeating the complete blood count with differential and reviewing previous blood counts whenever available. The temporal relationship between ATD initiation and the fall in neutrophil count should then be assessed. Abrupt development of profound neutropenia after exposure to carbimazole, methimazole or propylthiouracil strongly supports a drug-induced mechanism, particularly when other cell lines are preserved and no alternative cause is identified [3, 5, 6]. Conversely, pancytopenia, persistent neutropenia predating ATD exposure, abnormal peripheral blood morphology or failure of neutrophil recovery after drug withdrawal should prompt investigation for other causes [4-6, 31].

Constitutional and ethnic neutropenia

Some individuals have chronically low neutrophil counts without increased susceptibility to infection [31, 32]. Constitutional or ethnic neutropenia is particularly relevant in individuals of African, Middle Eastern or certain Mediterranean ancestries. Familial forms of neutropenia may also present with persistently reduced ANC. These conditions are generally characterized by long-standing stable neutropenia rather than an abrupt decline after drug exposure. Previous complete blood counts are therefore particularly useful when evaluating a patient with suspected ATD-induced agranulocytosis [30, 31].

Infectious causes

Acute infections, particularly viral infections, can produce transient or profound neutropenia and should be considered whenever neutropenia develops with fever or systemic symptoms. Relevant viral causes include Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Human Immunodeficiency Virus (HIV), hepatitis viruses and, in appropriate clinical settings, parvovirus B19 [31, 32]. Severe bacterial infection and sepsis may also be accompanied by neutropenia, particularly when consumption of neutrophils exceeds marrow production [31].

The epidemiological and geographical context should guide investigation for less common infections. Depending on travel history and exposure, malaria, visceral leishmaniasis, brucellosis and typhoid fever may need to be considered. Tuberculosis may be associated with cytopenias through several mechanisms, including marrow involvement, hypersplenism and inflammatory disease. In a

febrile patient with profound neutropenia, however, infection may be both the cause and the consequence of neutropenia, making the distinction particularly challenging.

Hematological disorders

Acute leukemia and myelodysplastic syndromes should be considered, particularly in older patients, when neutropenia is persistent, unexplained or associated with anemia, thrombocytopenia, macrocytosis or abnormalities on the peripheral blood smear [31, 32]. Bone marrow disorders may initially present with isolated neutropenia and can therefore mimic drug-induced agranulocytosis [31, 33].

Other rare hematological causes include pure white-cell aplasia, large granular lymphocytic leukemia or T-cell large granular lymphocytic expansions, and Paroxysmal Nocturnal Hemoglobinuria (PNH). The latter should be considered particularly when neutropenia is accompanied by hemolysis, thrombosis, pancytopenia or other suggestive clinical findings. Bone marrow examination is not systematically required in an otherwise typical case of ATD-induced agranulocytosis with prompt recovery after drug withdrawal, but it becomes appropriate when the clinical course is atypical or recovery is delayed.

Autoimmune neutropenia

Autoimmune neutropenia is an important alternative diagnosis in patients with autoimmune thyroid disease because autoimmune disorders frequently coexist [31, 32]. Systemic Lupus Erythematosus (SLE), Sjögren syndrome and rheumatoid arthritis may be associated with immune-mediated neutropenia. Felty syndrome, characterized by rheumatoid arthritis, neutropenia and splenomegaly, represents a particularly relevant differential diagnosis in patients with established rheumatoid arthritis [32].

Large granular lymphocytic disorders may also overlap clinically and biologically with autoimmune neutropenia. Anti-neutrophil antibodies can support an immune-mediated mechanism, but their sensitivity and specificity are limited and a negative test does not exclude autoimmune neutropenia. Consequently, laboratory immunological testing should be interpreted within the overall clinical context rather than used as a stand-alone diagnostic test.

Nutritional deficiencies

Nutritional deficiencies should be considered, particularly when neutropenia is associated with anemia, macrocytosis or other cytopenias [31, 32]. Vitamin B12 and folate deficiency can impair hematopoiesis and occasionally produce severe neutropenia, although pancytopenia or multilineage cytopenia is more typical of advanced deficiency. Vitamin B12 deficiency may be particularly relevant in patients with autoimmune thyroid disease because autoimmune clustering increases the likelihood of autoimmune gastritis and pernicious anemia. Malabsorption, including coeliac disease, should also be considered when the clinical context is suggestive [31, 32].

Other nutritional abnormalities, including severe copper deficiency, may produce neutropenia and should be considered in selected patients, particularly after gastrointestinal or bariatric surgery or in the presence of malabsorptive disorders.

Other medications and toxic exposures

Concomitant medications are a critical component of the differential diagnosis because patients receiving ATDs may be

exposed to several other drugs capable of causing neutropenia or agranulocytosis [31, 32]. Well-established examples include clozapine, ticlopidine, sulfasalazine and trimethoprim-sulfamethoxazole. Other antimicrobials, antiepileptic drugs and several additional medications have also been implicated [6, 8].

Dipyrone (metamizole) is particularly relevant in European practice because it is a well-recognized cause of idiosyncratic agranulocytosis. Beta-lactam antibiotics and other anti-infective agents can also cause neutropenia, usually after repeated or prolonged exposure, although the mechanisms and latency may differ from those of thionamide-associated agranulocytosis.

A complete medication history should therefore include prescription drugs, recently discontinued medications, over-the-counter preparations and, when relevant, herbal or complementary products. Particular attention should be paid to drugs introduced during the weeks preceding the neutropenic episode. Establishing a chronological medication timeline is often more informative than relying solely on the number of concomitant drugs.

Assessing Imputability: Establishing A Causal Relationship with the ATD

Attribution of severe neutropenia to an ATD requires more than the identification of concomitant exposure. Because agranulocytosis is a rare but potentially fatal adverse drug reaction and patients with Graves' disease may receive several medications, drug imputability should be assessed systematically. The objective is to determine whether the ATD is the most plausible cause after considering the chronology, clinical phenotype, alternative explanations and subsequent course.

The chronological relationship is the first component of imputability. The onset of neutropenia should be compatible with the known latency of ATD-induced agranulocytosis, with most cases occurring during the first weeks to three months of treatment [8, 18]. Previous exposure to the same ATD is particularly informative because sensitization may shorten the latency on re-exposure. Conversely, neutropenia that clearly preceded ATD initiation substantially weakens the causal attribution [11, 25].

The semiological and biological pattern constitutes the second component. An abrupt, profound and relatively isolated fall in neutrophils, particularly with preservation of hemoglobin and platelet counts, is compatible with ATD-induced agranulocytosis. The presence of fever, pharyngitis, tonsillitis or documented infection is supportive of the clinical syndrome but does not by itself establish drug causality. Conversely, pancytopenia, blasts or dysplastic cells on the peripheral smear, marked splenomegaly or other abnormalities suggesting marrow disease should reduce the probability of an isolated ATD-induced reaction.

The third component is the search for alternative causes. All recently introduced medications should be reviewed and their respective latency and known hematological toxicity considered. Viral infections, severe bacterial infection, autoimmune neutropenia, nutritional deficiencies, hematological malignancies and constitutional neutropenia should be investigated according to the clinical context. In patients receiving multiple potentially myelotoxic or agranulocytosis-inducing drugs, attribution to the ATD alone may remain uncertain.

The dechallenge, defined as hematological recovery after

withdrawal of the suspected drug, provides an important additional argument. Recovery of the ANC after ATD discontinuation supports causality, particularly when it occurs without treatment directed at another underlying cause. However, dechallenge should be interpreted cautiously because spontaneous recovery may occur and because G-CSF, antibiotics and other supportive interventions can modify the time course. Conversely, persistent severe neutropenia despite withdrawal should prompt reconsideration of the diagnosis and investigation for alternative or additional causes.

Rechallenge is generally inappropriate after true ATD-induced agranulocytosis. Although recurrence after re-exposure would provide strong evidence of causality, deliberate rechallenge is ethically unacceptable given the potentially life-threatening nature of the reaction. Consequently, absence of rechallenge does not weaken the diagnosis in routine clinical practice. Unintentional re-exposure resulting in recurrent neutropenia, when documented, constitutes particularly strong evidence of causality but should be regarded as an adverse event rather than a diagnostic strategy.

In patients exposed to several drugs, formal pharmacovigilance approaches can be useful. The French imputability method, as well as structured approaches such as the Naranjo algorithm, incorporates chronological and semiological criteria to classify the probability that a medication caused an adverse event. These tools may facilitate standardized reporting but should not replace clinical judgement. Their limitations are particularly relevant for idiosyncratic agranulocytosis, for which the event is rare, alternative drugs may be numerous, and rechallenge is usually contraindicated.

A practical assessment of ATD imputability should therefore integrate five elements: (1) compatible exposure and latency; (2) a characteristic hematological phenotype; (3) exclusion of competing causes; (4) recovery after withdrawal; and (5) absence or presence of previous exposure and, when it occurs inadvertently, recurrence on re-exposure. The greater the concordance between these domains, the stronger the causal attribution.

Distinguishing ATD-induced agranulocytosis from alternative causes

The diagnosis of ATD-induced agranulocytosis is ultimately a clinical diagnosis of probability supported by the temporal relationship between exposure and neutropenia, the depth of the ANC reduction, exclusion of competing causes and recovery after withdrawal [31-42]. Several features increase the probability of an ATD-induced mechanism: previously normal blood counts, abrupt development of severe isolated neutropenia, onset during the recognized risk period after ATD initiation, absence of another recently introduced high-risk medication and subsequent neutrophil recovery after discontinuation.

Conversely, persistent neutropenia despite withdrawal, pancytopenia, dysplastic changes, splenomegaly, abnormal lymphocyte populations or evidence of systemic autoimmune disease should prompt broader investigation. In patients with severe neutropenia and fever, the diagnostic evaluation must proceed in parallel with emergency management of possible infection and should never delay withdrawal of the suspected ATD.

The differential diagnosis is particularly important because attribution of neutropenia to an ATD has major therapeutic consequences [33-39]. Once true ATD-induced agranulocytosis has been established, re-exposure to the offending drug should generally

be avoided, and alternative definitive treatment of the underlying hyperthyroidism should be considered. Conversely, premature attribution of every episode of mild or moderate neutropenia to an ATD may unnecessarily deprive patients of an effective treatment. The diagnostic objective is therefore not merely to identify a temporal association, but to establish the most plausible causal relationship while simultaneously excluding potentially treatable alternative etiologies.

Management

Immediate measures: Immediate withdrawal of the suspected ATD is the cornerstone of management when severe neutropenia or agranulocytosis is suspected [3, 4, 16]. The drug should be discontinued without waiting for the results of extensive investigations when the clinical and hematological findings are strongly suggestive. All concomitant medications with a recognized potential to cause neutropenia or agranulocytosis should be reviewed, and non-essential potentially hematotoxic drugs should be discontinued whenever possible [4-6].

A complete blood count with differential should be repeated to confirm the severity of neutropenia and followed serially until hematological recovery. The initial evaluation should include assessment for fever, hemodynamic instability and clinically apparent infection, together with appropriate microbiological investigations. Blood cultures should be obtained promptly in febrile patients, without delaying empirical antimicrobial therapy.

ATD-induced agranulocytosis should be reported to the appropriate national pharmacovigilance system because systematic reporting is essential for maintaining reliable estimates of incidence, identifying new risk factors and improving understanding of drug-specific and population-specific susceptibility.

Once true ATD-induced agranulocytosis has been established, the implicated thionamide should not be restarted. Carbimazole and methimazole should be considered pharmacologically closely related because carbimazole is converted to methimazole. Switching from carbimazole to methimazole therefore does not represent a meaningful strategy to avoid recurrence. The use of propylthiouracil after carbimazole/methimazole-induced agranulocytosis is also generally discouraged because cross-reactive adverse reactions have been documented and because alternative treatments for Graves' disease are available [1-3, 5, 6].

The underlying thyrotoxicosis should subsequently be managed using a non-thionamide strategy whenever possible. Depending on the clinical situation, definitive treatment with radioactive iodine or thyroidectomy should be discussed. During the acute period, beta-blockade can provide symptomatic control of adrenergic manifestations. In selected patients with severe thyrotoxicosis, other short-term measures, including iodine administration and glucocorticoids, may be considered according to the clinical context and the presence of thyroid storm or impending thyroid storm [1-3].

Infection management and antibiotic therapy

Fever in a patient with an ANC $<0.5 \times 10^9/L$ should be considered a medical emergency. Such patients generally require urgent hospital assessment and, when clinically appropriate, admission for empirical broad-spectrum antimicrobial therapy. Blood cultures and other relevant microbiological samples should be obtained promptly, but antimicrobial treatment should not be delayed while awaiting microbiological results.

The choice of empirical antimicrobial therapy should follow contemporary febrile-neutropenia principles and local epidemiology rather than relying exclusively on older ATD-specific microbiological series. Antipseudomonal coverage is appropriate for patients with severe neutropenia and suspected bacterial infection, particularly in patients who are clinically unstable or have healthcare-associated risk factors. An antipseudomonal β -lactam such as piperacillin-tazobactam, cefepime or ceftazidime may be used according to local protocols, resistance patterns and patient-specific factors. Carbapenems may be appropriate in selected patients at high risk for infection with extended-spectrum β -lactamase-producing organisms. Additional agents should be guided by the clinical syndrome, microbiological findings and severity of illness.

The microbiological spectrum reported in ATD-induced agranulocytosis includes Gram-negative and Gram-positive organisms, with *Pseudomonas aeruginosa* historically identified as an important pathogen [33]. However, the evidence base is limited by the small size and age of ATD-specific microbiological series. Empirical therapy should therefore be based on contemporary institutional and national recommendations for high-risk febrile neutropenia rather than on a fixed antibiotic combination derived from historical ATD cohorts [34, 35].

Combination therapy with an aminoglycoside or fluoroquinolone should not be considered mandatory for all patients. Additional Gram-negative coverage may be justified in selected patients with hemodynamic instability, severe sepsis, documented resistant organisms or other high-risk features. Antimicrobial therapy should subsequently be narrowed according to microbiological results and clinical evolution.

Afebrile patients with profound neutropenia may also require hospital admission when additional high-risk characteristics are present, including significant comorbidity, prolonged or rapidly worsening neutropenia, hemodynamic instability, poor oral intake, inadequate social support or evidence of an occult infection.

Routine prophylactic antibiotics are not established for short-duration, non-chemotherapy drug-induced agranulocytosis and should not substitute for prompt treatment of fever or infection [3]. Protective isolation is likewise not routinely required, although standard infection-prevention measures should be applied. Granulocyte transfusion has no established routine role and should be reserved for exceptional, life-threatening infections in highly selected circumstances when conventional treatment is failing [4, 34, 35].

Corticosteroids should not be used routinely to treat ATD-induced agranulocytosis. Available clinical evidence has not demonstrated a convincing hematological benefit, and corticosteroids may increase infectious risk [34]. Their use should therefore be restricted to another established indication, such as thyroid storm, adrenal insufficiency or a specific immune-mediated disorder [5, 6].

Hematopoietic growth factors: evidence and indications

G-CSF is the principal hematopoietic growth factor investigated in ATD-induced agranulocytosis. The rationale is to accelerate neutrophil recovery by stimulating proliferation and maturation of granulocytic progenitors. However, the evidence base remains limited and consists predominantly of small observational studies, with only one small randomized trial specifically addressing ATD-induced agranulocytosis.

Fukata *et al.*, conducted a randomized study involving 24 patients and did not demonstrate a significant reduction in the duration of agranulocytosis with G-CSF [35]. Interpretation of this study is limited by its small sample size and by the relatively low G-CSF doses used. Subsequent observational studies using more conventional doses have suggested more rapid hematological recovery [36].

In a French reference-center study, Andrès *et al.*, reported 20 cases of ATD-related severe neutropenia or agranulocytosis treated with G-CSF and observed shorter hematological recovery and hospitalization compared with historical or contemporaneous patients managed without G-CSF [36]. In the Japanese series of Tajiri *et al.*, G-CSF was administered to 34 of 109 patients and was associated with an approximately two-day reduction in the duration of agranulocytosis [8]. These findings support a potential benefit of G-CSF, although the non-randomized nature of most available evidence prevents a definitive conclusion regarding mortality or major infectious outcomes [17, 37, 38].

Current clinical practice therefore generally considers G-CSF in patients with profound agranulocytosis, particularly when the ANC is $<0.5 \times 10^9/L$ and when fever, documented infection, severe comorbidity, advanced age or a prolonged expected duration of neutropenia is present [5, 6]. The decision should be individualized according to disease severity and local hematological practice [5, 38].

A commonly used dose is filgrastim 5 $\mu g/kg/day$ administered subcutaneously, with higher doses, up to approximately 10 $\mu g/kg/day$, used in selected severe cases. Treatment is generally continued until clear neutrophil recovery, rather than according to an inflexible numerical threshold. A practical target is an ANC $>1.0 \times 10^9/L$ with a sustained upward trajectory; treatment may subsequently be discontinued according to clinical response and local protocol [5, 8, 36-38].

The available evidence does not establish that G-CSF prevents mortality or infectious complications in all patients. Its principal potential benefit is acceleration of neutrophil recovery, which may shorten the period of profound immunological vulnerability and possibly reduce hospitalization. G-CSF should therefore be regarded as an adjunct to, rather than a substitute for, immediate ATD withdrawal, appropriate antimicrobial therapy and supportive care.

Rechallenge and Cross-Reactivity

Rechallenge with the causative ATD after confirmed agranulocytosis is generally contraindicated. Although recurrence after re-exposure would provide strong evidence of causality, deliberate rechallenge is ethically inappropriate because recurrent agranulocytosis may occur rapidly and can be fatal. Consequently, the absence of rechallenge does not weaken the diagnosis in clinical practice.

Carbimazole and methimazole require particular consideration because they are pharmacologically linked: carbimazole is rapidly converted to methimazole. A patient who has developed agranulocytosis attributed to carbimazole should therefore not be switched to methimazole as a strategy to avoid recurrence. They should be considered essentially the same pharmacological exposure with respect to the relevant active thionamide.

PTU is chemically distinct from carbimazole/methimazole, but cross-reactive adverse reactions have been reported. Earlier studies suggested cross-reactivity between thionamides in approximately

15% of patients experiencing adverse reactions; importantly, this estimate refers to adverse reactions overall and should not be interpreted as a 15% recurrence rate for agranulocytosis [22, 30]. The precise frequency of cross-reactive agranulocytosis remains uncertain because of the rarity of the event and the small number of patients who have been re-exposed [5, 26].

The practical implication is nevertheless important: after unequivocal ATD-induced agranulocytosis, treatment with another thionamide should generally be avoided whenever effective non-thionamide alternatives are available [1, 2, 6]. Radioactive iodine or thyroidectomy should therefore be considered as definitive treatment of Graves' disease. The choice depends on age, disease characteristics, goitre size, ophthalmopathy, pregnancy status, patient preference and local expertise [2, 3, 5].

The situation differs after less severe adverse reactions. A mild, transient and unexplained neutropenia should not automatically be equated with agranulocytosis, and a non-hematological intolerance such as a minor cutaneous reaction does not necessarily preclude the use of another ATD. The decision must be based on the nature, severity and certainty of the initial adverse reaction.

Previous ATD-induced agranulocytosis should also be clearly documented in the patient's medical record as a serious drug allergy or adverse drug reaction, with the implicated molecule explicitly identified. Patients should be informed that re-exposure to the culprit drug is contraindicated and should be advised to report this history before receiving future antithyroid treatment.

Definitive Management of Hyperthyroidism After Agranulocytosis

Once ATD-induced agranulocytosis has occurred, the therapeutic strategy for the underlying hyperthyroidism must be reconsidered. In Graves' disease, radioactive iodine and thyroidectomy are the principal definitive alternatives to thionamide therapy [1, 2]. The choice should be individualized and may require multidisciplinary discussion between endocrinology, nuclear medicine and endocrine surgery [2, 3].

Radioactive iodine is an effective definitive treatment for many patients but may be inappropriate in selected circumstances, including pregnancy and breastfeeding. Thyroidectomy provides rapid definitive control and may be particularly attractive in patients with a large goitre, suspicious thyroid nodules, severe hyperthyroidism requiring rapid definitive treatment, or contraindications to radioactive iodine.

During the interval between ATD withdrawal and definitive treatment, symptomatic control can generally be achieved with beta-blockers. In severe thyrotoxicosis, additional measures may be required, including iodine, glucocorticoids, cholestyramine or other interventions according to the severity and clinical context [1-3].

Thus, management of ATD-induced agranulocytosis extends beyond correction of the neutrophil count. The immediate objectives are withdrawal of the offending drug, prevention and treatment of infection, and acceleration of hematological recovery when indicated. The subsequent objective is to achieve durable control of hyperthyroidism without exposing the patient again to a potentially life-threatening thionamide reaction.

Monitoring and Prevention

Routine hematological monitoring during ATD therapy

remains controversial. Agranulocytosis may develop abruptly, and a previously normal blood count does not reliably exclude subsequent severe neutropenia. Conversely, several observational studies have shown that scheduled granulocyte monitoring can identify a substantial proportion of cases before the development of clinically overt infection. In a Japanese cohort of 25 patients with ATD-induced agranulocytosis, periodic granulocyte measurements detected 64% of cases, including nine asymptomatic and seven minimally symptomatic patients; among patients with less severe granulocytopenia, 94% were identified by scheduled monitoring. 36 Earlier series similarly reported that a considerable proportion of agranulocytosis episodes were detected before infectious symptoms became apparent [37]. These findings support the biological plausibility of surveillance, but they do not establish that routine monitoring reduces severe complications or mortality, and the applicability of these data to contemporary European practice remains uncertain [39-41].

Accordingly, major international guidelines have not endorsed a single universal schedule for serial blood counts during ATD therapy. The 2018 European Thyroid Association guideline emphasizes patient education and prompt differential blood-cell counting in patients who develop fever or pharyngitis, while noting that routine hematological monitoring is of uncertain value because agranulocytosis can occur suddenly [3]. The American Thyroid Association similarly emphasizes symptom-triggered assessment rather than routine serial complete blood counts [4]. Importantly, this position should not be interpreted as evidence that blood-count monitoring is ineffective; rather, the available studies have not demonstrated that a specific surveillance schedule provides a clinically meaningful outcome advantage over rapid symptom-triggered testing [2, 3].

A pragmatic prevention strategy should therefore combine a baseline assessment, structured patient education, rapid symptom-triggered testing, and selective additional hematological surveillance. A complete blood count with differential should be obtained before initiating ATD therapy, both to document the baseline ANC and to identify pre-existing neutropenia that may complicate subsequent interpretation. During treatment, patients should receive explicit written and verbal instructions to stop the ATD and obtain an urgent blood count if they develop fever, sore throat, pharyngitis, mouth ulcers, or other symptoms suggestive of infection. This recommendation is particularly important during the first 2-3 months, when the incidence of agranulocytosis is highest, but vigilance should be maintained throughout treatment because late-onset cases can occur [2, 3].

In clinical practice, periodic differential blood counts may reasonably be considered during the early treatment period in selected patients, particularly when access to urgent laboratory testing is limited, adherence to symptom-based instructions is uncertain, the patient has relevant comorbidities, or local practice and healthcare infrastructure permit inexpensive repeated testing. However, a rigid schedule such as weekly testing for 12 weeks followed by monthly testing for one year should be regarded as a pragmatic institutional strategy rather than an evidence-based international standard. In populations in which periodic monitoring is routinely implemented, the differential count — and specifically the ANC — should be assessed rather than relying solely on the total leukocyte count, because agranulocytosis may occasionally occur despite a relatively preserved total white-cell count [40, 41].

The distinction between prevention and early detection is

clinically important. No laboratory surveillance strategy can reliably prevent ATD-induced agranulocytosis because the underlying event is usually idiosyncratic and may evolve rapidly. The most effective preventive intervention remains patient education combined with immediate discontinuation of the suspected ATD when clinically significant neutropenia or compatible infectious symptoms occur. Once agranulocytosis is suspected, treatment should not be delayed while awaiting a scheduled monitoring appointment. Fever or pharyngitis in a patient receiving an ATD should trigger an urgent complete blood count with differential and, when severe neutropenia is confirmed, immediate management according to the principles outlined above [2, 3, 40].

Pharmacogenomics represents a potentially important future approach to prevention. The identification of strong associations between ATD-induced agranulocytosis and HLA-B*38:02/HLA-DRB1*08:03 in Asian populations, and HLA-B*27:05 in European populations, raises the possibility of identifying individuals at substantially increased genetic risk before treatment [40, 41]. However, these associations are strongly population-dependent, and their positive predictive value in unselected clinical populations remains insufficient to justify universal screening. The optimal strategy may ultimately involve population-specific panels combining HLA variants with clinical characteristics, drug dose, and other genetic markers. Until prospective studies demonstrate clinical utility, cost-effectiveness, and an improvement in patient outcomes, routine pharmacogenomic screening should remain investigational outside appropriately selected populations or research programs [15, 18, 19, 23].

Overall, prevention of ATD-induced agranulocytosis should not rely on blood-count surveillance alone. Baseline hematological assessment, explicit patient education, rapid symptom-triggered differential blood counting, avoidance of re-exposure after confirmed agranulocytosis, and appropriate consideration of definitive therapy constitute the current core of prevention. Periodic granulocyte monitoring may provide an additional safety layer in selected settings, but its frequency should be individualized rather than presented as a universally established schedule.

Prognosis and Mortality Trends

The prognosis of ATD-induced agranulocytosis has improved substantially over the past several decades, although mortality remains clinically relevant and should not be considered negligible. Historical series reported mortality rates as high as 17-18%. In a Swedish series published in the 1970s, 5 of 29 patients with ATD-induced agranulocytosis died (17%), whereas subsequent studies from the 1980s reported mortality rates of approximately 2% [8, 20]. More contemporary data nevertheless indicate that fatal outcomes continue to occur. In the largest published series, comprising 754 cases collected over 30 years in Japan, 30 patients died, corresponding to an overall case-fatality rate of approximately 4%. Importantly, the analysis of these fatal cases suggested that some deaths might have been preventable, particularly when recognition of symptoms and diagnosis of agranulocytosis were delayed [11, 25, 39].

More recent specialist-center experience suggests that outcomes can be favorable when ATD withdrawal, infection management, hematological support, and definitive treatment of hyperthyroidism are rapidly coordinated. In the Strasbourg cohort of 30 patients with severe ATD-induced neutropenia or agranulocytosis, two patients

died, corresponding to a mortality rate of 6.6%; both deaths occurred in elderly patients with severe infectious complications [20]. These observations emphasize that mortality estimates are highly dependent on case definition, referral patterns, patient age and comorbidity, severity of neutropenia, infectious complications, and access to specialist care. Consequently, a universal contemporary mortality rate of <2% cannot currently be considered established [25].

Age is one of the most consistently reported adverse prognostic factors. In the literature reviewed by Andrès et al., mortality was substantially higher among patients aged ≥ 65 years than among younger patients (13.8% vs 1.2%; RR 12.9, 95% CI 1.45-114.9) [20]. The excess risk in older patients is likely multifactorial, reflecting a higher prevalence of cardiovascular and other comorbidities, impaired physiological reserve, increased susceptibility to severe infection, and potentially delayed recognition of atypical infectious presentations. Severe neutropenia itself is also an important determinant of outcome, particularly when the ANC falls below $0.1 \times 10^9/L$ and remains suppressed for several days [25].

The development of sepsis, septic shock, or pneumonia represents a major adverse prognostic event. In the Strasbourg series, septicemia, pneumonia, and septic shock were prominent clinical complications, and both fatal cases occurred in the setting of severe infection [20]. The large Japanese series similarly identified delayed recognition and delayed medical assessment as potentially preventable contributors to fatal outcome [22]. These findings reinforce the importance of immediate blood-count assessment in any ATD-treated patient presenting with fever, pharyngitis, mucosal ulceration, or other symptoms compatible with infection [11, 25].

The role of G-CSF in improving prognosis remains less certain than its effect on hematological recovery. Observational studies have associated G-CSF administration with more rapid neutrophil recovery and shorter hospitalization, including the Strasbourg cohort, in which hematological recovery occurred significantly faster among patients receiving hematopoietic growth factors [20]. However, available studies are small, heterogeneous, and largely observational, and a definitive reduction in mortality attributable to G-CSF has not been demonstrated. G-CSF should therefore be regarded as an important component of supportive management in selected patients with profound or prolonged agranulocytosis, particularly when severe infection or other high-risk features are present, rather than as an intervention with proven independent survival benefit [25, 36, 38].

Overall, the major determinants of outcome appear to be early recognition, immediate withdrawal of the offending ATD, rapid identification and treatment of infection, severity and duration of neutropenia, patient age and comorbidity, and access to coordinated specialist care. The progressive reduction in mortality over time probably reflects improvements across this entire management pathway rather than the introduction of any single intervention. Prevention of diagnostic delay - through explicit patient education and immediate differential blood-cell counting when warning symptoms occur - therefore remains one of the most important potentially modifiable determinants of survival.

Conclusions, What Is New for The Clinician, and Future Research Priorities

ATD-induced agranulocytosis remains an uncommon but potentially fatal complication of methimazole, carbimazole, and propylthiouracil therapy. Its clinical importance is disproportionate

to its incidence because the onset may be abrupt, previously normal blood counts do not reliably exclude subsequent agranulocytosis, and severe infection may develop before the diagnosis is established. The contemporary approach should therefore move beyond the traditional concept of a rare drug reaction towards a structured model integrating individual susceptibility, drug exposure, early clinical recognition, rapid biological confirmation, and coordinated definitive management of hyperthyroidism.

What is new for the clinician?

Several findings from the contemporary literature have direct practical implications. First, terminology and severity should be standardized. Neutropenia should be graded according to the ANC, with mild neutropenia generally defined as $1.0-1.5 \times 10^9/L$, moderate neutropenia as $0.5-1.0 \times 10^9/L$, and severe neutropenia as $<0.5 \times 10^9/L$. The term agranulocytosis should be reserved for profound neutropenia, conventionally an ANC $<0.5 \times 10^9/L$, and particularly for values $<0.1 \times 10^9/L$ when describing very severe disease. Consistent terminology is essential for clinical communication, pharmacovigilance, and comparison between studies.

Second, ATD-induced agranulocytosis is not simply a class effect of equal magnitude across all patients and all treatment regimens. Risk appears to depend on the molecule, dose, treatment duration, ethnicity, genetic background, and individual susceptibility. Methimazole dose is a potentially modifiable determinant, with historical evidence indicating a substantially higher risk at doses >40 mg/day. This supports the use of the lowest effective ATD dose, particularly during initiation and dose escalation. However, dose reduction cannot eliminate the risk because idiosyncratic agranulocytosis may occur at conventional or low doses.

Third, pharmacogenomics has transformed the understanding of individual susceptibility. Strong associations have been demonstrated between ATD-induced agranulocytosis and HLA-B*38:02/HLA-DRB1*08:03 in several Asian populations and HLA-B*27:05 in European populations [40,41]. Additional variants, including HLA-B*39:01 in Japanese populations and potentially rare variants affecting neutrophil biology such as NOX3, broaden the biological framework. These findings establish a genetic component to susceptibility but do not yet justify universal pre-treatment screening across populations. Their future clinical value will depend on prospective validation, population-specific predictive performance, cost-effectiveness, and demonstration that genotype-guided treatment improves patient outcomes [15, 18, 19, 23, 27].

Fourth, true ATD-induced agranulocytosis should be regarded as a contraindication to re-exposure. Carbimazole and methimazole are pharmacologically closely related because carbimazole is converted to methimazole, and switching between them after confirmed agranulocytosis is therefore inappropriate. Although propylthiouracil is chemically distinct, cross-reactive adverse reactions have been reported. The frequently quoted figure of approximately 15% refers to cross-reactive adverse reactions to thionamides overall and should not be interpreted as the incidence of cross-reactive agranulocytosis. After unequivocal agranulocytosis, definitive treatment with radioiodine or thyroidectomy is generally preferable to exposure to another thionamide whenever clinically feasible.

Fifth, G-CSF has an established role in selected severe cases but its benefit should not be overstated. Observational studies consistently suggest more rapid neutrophil recovery and shorter hospitalization

in some patients receiving G-CSF, whereas small controlled studies have produced less definitive results. G-CSF is therefore particularly reasonable in profound, prolonged, or complicated agranulocytosis, especially in patients with infection, advanced age, major comorbidity, or a high risk of infectious complications. Its independent effect on mortality has not been established.

Sixth, prevention depends more on rapid recognition than on any single laboratory-monitoring schedule. Baseline blood-cell counts, explicit patient education, and immediate differential blood counting when fever, sore throat, pharyngitis, oral ulceration, or other infectious symptoms develop should constitute the minimum safety framework. Periodic granulocyte monitoring can detect some asymptomatic cases and may be appropriate in selected healthcare settings, but weekly monitoring for 12 weeks followed by monthly monitoring for one year should not be presented as a universally evidence-based international standard [2, 3, 40, 41].

Finally, prognosis has improved but remains heterogeneous. Historical mortality was substantially higher than in contemporary series, but fatal cases continue to occur, particularly among older patients and those presenting with profound neutropenia, pneumonia, septicemia, or septic shock. The improvement in outcomes is best understood as the consequence of earlier recognition, immediate withdrawal of the offending drug, modern antimicrobial therapy, supportive hematological care, and rapid transition to definitive treatment of hyperthyroidism rather than the effect of G-CSF alone.

A ten-year research agenda

The next phase of research should move from retrospective case series towards prospective, multinational, phenotype-rich cohorts. Five complementary priorities could substantially improve the prevention and management of ATD-induced agranulocytosis.

Establish harmonized definitions and prospective surveillance. International centers should adopt common definitions for neutropenia, agranulocytosis, severe infection, recovery, and mortality, while prospectively recording ATD molecule, dose, treatment duration, previous ATD exposure, concomitant medications, baseline ANC, ethnicity, comorbidities, and infectious complications. Such registries would provide reliable denominators and allow absolute rather than pharmacovigilance-derived risks to be estimated.

Develop European pharmacogenomic validation cohorts. HLA-B*27:05, HLA-B*38:02, HLA-DRB1*08:03, HLA-B*39:01 and other candidate variants should be evaluated prospectively in large European populations. Particular attention should be paid to whether genetic predictors discriminate true agranulocytosis from milder neutropenia. Models combining genotype with age, sex, ATD dose, baseline blood counts, previous exposure, and clinical characteristics may ultimately outperform HLA testing alone.

Define the optimal monitoring strategy. A pragmatic randomized or cluster-randomized study comparing symptom-triggered monitoring with structured periodic ANC surveillance could determine whether routine testing reduces severe infection, intensive-care admission, hospitalization, or mortality. Digital patient education, electronic alerts, home blood-count testing, and automated laboratory notification could be incorporated into such a trial. The objective should not simply be to detect more cases, but to determine whether earlier detection changes clinically meaningful outcomes.

Refine treatment of established agranulocytosis. Prospective comparative studies should clarify which patients benefit from G-CSF, the optimal dose and duration, and whether early administration improves clinically relevant outcomes rather than only shortening neutropenia. Parallel studies should evaluate antimicrobial strategies, predictors of invasive infection, and criteria for outpatient versus inpatient management in afebrile profound neutropenia.

Develop individualized ATD prescribing and definitive-treatment pathways. Integrating pharmacogenomics, drug dose, clinical phenotype, comorbidity, and patient preferences could support individualized selection between methimazole/carbimazole, propylthiouracil, radioiodine, and surgery. Health-economic analyses will be essential to determine whether pre-treatment HLA screening, enhanced blood-count surveillance, or combined risk-stratification algorithms are cost-effective in different healthcare systems.

Perspectives

The future management of ATD-induced agranulocytosis is therefore likely to shift from a predominantly reactive model towards predictive and personalized prevention. The immediate clinical priorities remain simple: use the lowest effective ATD dose, educate every patient about alarm symptoms, obtain an urgent ANC when symptoms occur, discontinue the suspected drug immediately when agranulocytosis is suspected or confirmed, treat infection without delay, and avoid thionamide re-exposure after unequivocal agranulocytosis. The longer-term objective is to identify, before treatment, those patients in whom the risk is sufficiently high to justify an alternative therapeutic strategy or enhanced monitoring.

The principal evidence gap is now geographical as well as methodological. Much of the pharmacogenomic evidence originates from East Asian populations, whereas European clinical practice includes substantial use of carbimazole and different prescribing patterns. Large European and international collaborative registries are consequently needed to establish absolute risks, validate genetic predictors across ancestries, and determine whether genotype-guided or intensified monitoring strategies improve outcomes. The combination of real-world pharmacovigilance, prospective clinical phenotyping, pharmacogenomics, and artificial intelligence-assisted risk prediction may ultimately permit a clinically actionable risk score before the first ATD prescription.

Thus, the key message for the clinician is not that ATD-induced agranulocytosis has become preventable, but that its consequences have become increasingly preventable. The decisive intervention remains recognition without delay. The next generation of research should determine whether that principle can be extended further - from early detection to reliable prediction and ultimately individualized prevention.

Acknowledgments

We would like to express our sincere gratitude to all patients whose clinical experiences and contributions have helped advance our understanding of antithyroid drug-induced neutropenia and agranulocytosis. Their trust and participation have been essential to the development of clinical knowledge in this field. We also warmly thank the clinicians, nurses, pharmacists, biologists, and other healthcare professionals of the University Hospital of Strasbourg (HUS, France) who have contributed to the diagnosis, management, monitoring, and follow-up of patients with neutropenia and agranulocytosis. Finally, we gratefully acknowledge all clinicians and researchers of the HUS

Study Group on Neutropenia and Agranulocytosis, whose clinical expertise, scientific collaboration, data collection, and continuous exchange have contributed substantially to this work. We particularly value the multidisciplinary approach that brings together internal medicine, hematology, endocrinology, pharmacology, biology, and other specialties involved in the care and investigation of these rare but potentially life-threatening drug-related disorders.

Conflicts of Interest

Professor Andrès has received research funding and honoraria from pharmaceutical companies involved in the development and commercialization of hematopoietic growth factors. The funding sources had no role in the design, conduct, interpretation, or writing of this review. All other authors declare no competing interests.

Author Contributions

E.A. and N.L.V. conceived the review and drafted the manuscript. K.S. contributed to the literature search, evidence extraction, and critical revision. J.E.T. and X.J. contributed to critical revision. All authors reviewed and approved the final version. ChatGPT and Claude AI were used for language editing and structural refinement; all scientific content, interpretation, and references were independently checked and approved by the authors.

Funding

No specific funding was received for this work.

Box 1: Literature Search Strategy

Objective: A structured literature search was undertaken to identify clinical, epidemiological, mechanistic, pharmacogenomic, and therapeutic evidence concerning antithyroid drug (ATD)-induced neutropenia and agranulocytosis.

Databases and sources: MEDLINE/PubMed, Embase, and the Cochrane Library were searched from database inception to **September 2026**. Additional records were identified by screening the reference lists of relevant reviews, guidelines, cohort studies, and pharmacovigilance reports. European and international clinical practice guidelines were also considered. Data of our research group on neutropenia in the University Hospital of Strasbourg (France) were added to the sources.

Search strategy: Search terms combined controlled vocabulary and free-text terms related to antithyroid drugs and hematological toxicity, including: *methimazole*, *thiamazole*, *carbimazole*, *propylthiouracil*, *antithyroid drugs*, *neutropenia*, *agranulocytosis*, *granulocytopenia*, *febrile neutropenia*, *drug-induced neutropenia*, *G-CSF*, *granulocyte colony-stimulating factor*, *HLA*, *pharmacogenomics*, *genetic susceptibility*, *monitoring*, and *mortality*. Boolean operators (AND/OR) were used to combine concepts.

Eligibility and selection: Priority was given to original observational studies, population-based cohorts, pharmacovigilance studies, clinical trials, pharmacogenomic studies, systematic reviews, meta-analyses, and international guidelines. Studies were considered particularly relevant when they provided quantitative estimates of incidence, risk factors, drug or dose effects, genetic susceptibility, clinical manifestations, management, monitoring, or outcomes. Historical landmark studies were retained when they provided unique epidemiological or mechanistic evidence. Case reports were

considered selectively for rare clinical presentations or recurrent agranulocytosis.

Evidence synthesis: Because of substantial heterogeneity in case definitions, populations, ATD exposure, dose, monitoring strategies, and outcome ascertainment, findings were synthesized qualitatively rather than subjected to a new quantitative meta-analysis. Particular attention was paid to distinguishing neutropenia from agranulocytosis separating absolute risk from relative risk, and distinguishing evidence directly demonstrated in ATD-induced agranulocytosis from evidence extrapolated from drug-induced neutropenia or febrile neutropenia in other clinical settings.

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