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Neutropenia and Agranulocytosis Induced by Antithyroid Drugs: Clinical Insights and Management

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Abstract

Background: Antithyroid Drugs (ATDs) are widely used for hyperthyroidism but can rarely cause idiosyncratic neutropenia and agranulocytosis, potentially leading to life-threatening infections.

Objective: To summarize the definition, epidemiology, clinical features, and management of ATD-induced neutropenia and agranulocytosis.

Methods: Review of international literature and local data from the University Hospitals of Strasbourg.

Results: Neutropenia is classified as moderate (ANC 1000–1500/mm^3), severe (<500/mm^3), or profound (<200/mm^3), while agranulocytosis corresponds to near-complete granulocyte depletion (ANC <100/mm^3). ATD-induced neutropenia usually occurs idiosyncratically within the first three months of therapy. Early clinical signs include fever >38.5°C and erythematous or ulcero-necrotic pharyngitis, with additional manifestations such as stomatitis, gingivitis, and systemic infections in advanced cases. Local data indicate seven cases per year; international series report incidences of 0.1–0.5%, primarily within 2-12 weeks of treatment. Risk factors include age >60 years, female sex, and possibly higher initial doses. Prompt recognition and immediate complete blood count are essential, as delayed diagnosis increases the risk of bacteremia, pneumonia, and septic shock. Management involves ATD discontinuation, infection control, and consideration of Granulocyte Colony-Stimulating Factor (G-CSF). Cross-reactivity between ATDs should guide alternative therapy.

Conclusion: Although rare, ATD-induced neutropenia and agranulocytosis are medical emergencies requiring early detection and adherence to international management guidelines to prevent severe outcomes.

Keywords: Antithyroid Drugs; Neutropenia; Agranulocytosis; Idiosyncratic Drug Reaction; Graves' Disease; Granulocyte Colony-Stimulating Factor-G-CSF; Clinical Management; Prevention

Introduction

Antithyroid Drugs (ATDs) constitute the first-line treatment for most forms of hyperthyroidism, particularly Graves' disease. The most widely prescribed molecules are thiamazole (methimazole), its prodrug carbimazole, and propylthiouracil. These agents are generally well tolerated, yet can occasionally trigger severe and unpredictable adverse reactions, including hepatotoxicity, vasculitis, and hematologic complications. Among the latter, neutropenia is of particular concern as it may progress to agranulocytosis, exposing patients to a major infectious risk.

This complication is difficult to anticipate: onset is typically sudden, often asymptomatic, and may arise several weeks after therapy initiation. For clinicians, awareness of its risk factors, early warning signs, and appropriate management strategies is essential, both to optimize patient safety and to minimize iatrogenic morbidity. In the broader context of personalized medicine, refining risk prediction and surveillance strategies represents a key objective.

This review aims to synthesize current knowledge for clinical practice, addressing successively the epidemiology, risk determinants, clinical and biological manifestations, microbiological findings, and therapeutic as well as preventive approaches. Finally, we highlight emerging perspectives, notably the contribution of artificial intelligence to individualized risk stratification and monitoring.

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Materials and Methods

This narrative review integrates published international data with a retrospective analysis of anonymized HUS cases (2010-2019), for which partial data have been previously published [1, 2]. Data included patient demographics, type of ATD, ANC, timing of neutropenia, presenting symptoms, management, and outcomes. According to French law (LoiJardé), no formal ethics committee approval was required for this retrospective analysis of anonymized data.

A comprehensive search of *PubMed*, *Scopus*, and *Google Scholar* was performed for articles published up to 2025, using keywords including "antithyroid drugs," "neutropenia," "agranulocytosis," "idiosyncratic reaction," and "Graves' disease." Relevant guidelines and position statements from international endocrine societies were also reviewed.

Definition, Classification and Epidemiology

Neutropenia is defined as a reduction in Absolute Neutrophil Count (ANC) and is classified as moderate (1000–1500/mm^3), severe (<500/mm^3), or profound (<200/mm^3),with agranulocytosis representing near-complete depletion of granulocytes (<100/mm^3), associated with high risk of severe infections [3, 4, 5]. Idiosyncratic ATD-induced neutropenia is unpredictable, not dose-dependent, and may result from immune-mediated mechanisms or direct bone marrow toxicity [3, 4, 6]. Moderate neutropenia (ANC 1000–1500/mm^3; 1-1.5×10^9/L) is associated with a moderate risk of infection, severe neutropenia (ANC <500/mm^3; <0.5×10^9/L) carries a high risk of infection, and profound neutropenia (ANC<200/mm^3; <0.2×10^9/L) exposes patients to a major risk of infection. Agranulocytosis, often used interchangeably with severe neutropenia, refers more precisely to near-complete depletion of the granulocytic lineage (ANC≈0/mm^3, theoretically <100/mm^3;<0.1×10^9/L), representing a potentially life-threatening infectious emergency.

Neutropenia induced by ATDs is most often idiosyncratic, meaning it is not dose-dependent and arises from immune-mediated mechanisms or direct bone marrow toxicity. Its onset is typically acute, sometimes abrupt, and classically occurs within the first three months of treatment.

ATD-induced agranulocytosis is an uncommon but well-documented complication, with a global incidence of 0.1-0.5% of treated patients. The risk is highest during the early phase of treatment, particularly between the second and twelfth week after initiation. Carbimazole and benzylthiouracil are the drugs most frequently implicated, although thiamazole and propylthiouracil are also reported. Older patients, especially those over 60 years, are at higher risk, and females are predominantly affected. While the relationship between drug dose and risk remains debated, several studies suggest that higher initial doses— such as methimazole above 15mg per day or carbimazole equivalents exceeding 30mg per day — may increase the likelihood of severe neutropenia or agranulocytosis.

Local data from the University Hospitals of Strasbourg indicate an average of seven cases of ATD-induced agranulocytosis per year. A retrospective series conducted between 2010 and 2019 identified 30 patients who developed severe neutropenia or agranulocytosis, most frequently associated with carbimazole and benzylthiouracil. Internationally, similar patterns have been observed: in Japan, an analysis of 754 cases collected over 30 years estimated an incidence of 0.1-0.15% among patients with Graves' disease, while in China, a large series of nearly 9,700 patients referred for radioiodine therapy identified 114 cases over 15 years, with the majority occurring within 8 to 12 weeks of treatment. More recent Japanese claims-database studies confirmed that leukopenia, including severe neutropenia, occurred more frequently during the first 72 days of therapy (0.7%), and the need for Granulocyte Colony-Stimulating Factor (G-CSF) was similarly concentrated in the early months.

Mortality rates, while variable, are not negligible, particularly when diagnosis is delayed. The clinical course is often abrupt and rapidly progressive, underscoring the importance of early recognition, close monitoring of ANC during the early treatment period, and prompt intervention.

Risk Factors and Vulnerable Populations

The incidence of ATD-induced agranulocytosis ranges from 0.1-0.5%, with most events occurring 2-12 weeks after therapy initiation [7, 8, 9, 10, 11, 12, 13]. Local HUS data indicate an average of 7 cases per year, while retrospective analyses and international series confirm similar patterns [8, 9, 11, 12]. Risk factors include older age (>60 years), female sex, and possibly higher initial doses of methimazole or carbimazole [7,10, 11, 13].

Several factors have been associated with an increased risk of ATD–induced neutropenia (Table 1). Advanced age is consistently recognized as a major determinant, with higher frequencies observed in patients over 60 years. This is likely related not only to age-related marrow vulnerability but also to the higher prevalence of comorbidities in this group. The concurrent use of other myelotoxic drugs — such as immunosuppressants prescribed for autoimmune diseases — further increases susceptibility.

Female sex has also been reported more frequently among affected patients. However, this observation may largely reflect the strong female predominance of Graves' disease itself rather than an independent biological risk factor.

Beyond demographic and clinical parameters, genetic predisposition has emerged as a key element, particularly in Asian populations. Large Japanese and Chinese cohort studies have identified specific Human Leukocyte Antigen (HLA) haplotypes, including HLA-B*38:02 and HLA-DRB1*08:03, as being strongly associated with ATD-induced agranulocytosis in patients treated with thiamazole. These findings suggest a possible role for pharmacogenetic screening in high-prevalence populations, enabling earlier identification of at-risk individuals.

In contrast, data from European cohorts remain less conclusive regarding genetic associations. In these populations, clinical factors such as older age, higher initial drug dose, and comorbidities appear to play a more prominent role in risk stratification. Together, these observations underline the multifactorial nature of ATD-induced neutropenia and highlight the importance of integrating demographic, clinical, and genetic data when tailoring treatment and monitoring strategies.

Clinical Presentation

ATD-induced neutropenia typically presents acutely, often with fever >38.5°C and erythematous or ulcero-necrotic pharyngitis, sometimes accompanied by stomatitis, gingivitis, oral ulcerations, or systemic infections such as pneumonia, skin infections, bacteremia, and septicemia [14, 15, 16, 17]. Severe cases may progress rapidly

Table 1: International recommendations for the management.

Management Aspect	Recommendation	International guidelines / Data
Incidence	0.1-0.5% of patients on antithyroid drugs (ATD) develop agranulocytosis	Europe, US, Asia
Immediate drug discontinuation	Stop ATD immediately upon suspicion	Strongly recommended by ATA (US), ETA (Europe), JTA (Japan)
Hospitalization	Recommended for absolute neutrophil count (ANC)< 500/μL or severe infection	Protective isolation optional for short-duration neutropenia
Outpatient management	Consider for asymptomatic, young, low-risk patients	Requires close follow-up; feasible per European and Japanese case series
Empirical antibiotics	Initiate broad-spectrum therapy promptly	Must cover multidrug-resistant organisms; supported by WHO and ATA guidelines
Hematopoietic growth factors (G-CSF)	Consider for ANC<100/μL, elderly, comorbidities, severe infection	Shown to shorten recovery time; not universally routine
Thyroid hormone replacement	Temporary levothyroxine to maintain euthyroidism	Recommended as a bridge before definitive therapy (surgery or radioactive iodine)
Pharmacovigilance reporting	Mandatory reporting of all cases	Ensures global monitoring; WHO, Europe andUSA guidelines

and can be life-threatening. The sudden onset of erythematous pharyngitis, occasionally ulcero-necrotic and notably without purulent exudate is highly characteristic. Other local manifestations may include stomatitis, gingivitis, or painful oral ulcerations, which are more frequent in profound neutropenia. In more advanced cases, systemic infections such as pneumonia, skin and soft tissue infections, or gastrointestinal infections may develop. Severe complications, including bacteremia, septicemia, and, rarely, septic shock, can occur when neutropenia is profound.

Case Illustration

A 45-year-old woman treated with carbimazole for Graves' disease presented with sudden high fever (39°C) and severe odynophagia. Examination revealed erythematous pharyngitis without exudate; ANC was 80/mm³ (0.08×10⁹/L). Broad-spectrum antibiotics and G-CSF were initiated, and the patient recovered after hospitalization [14, 15]. This case illustrates the abrupt onset, characteristic clinical presentation, and critical importance of early recognition and intervention.

In this context, an immediate Complete Blood Count (CBC) is mandatory to document the presence and severity of neutropenia. The rapidity of diagnosis directly affects prognosis, as the risk of severe infection rises substantially when neutrophil counts fall below 100/mm³ (<0.1×10⁹/L). Complications such as bacteremia, pneumonia, and septicemia are common, and exceptionally severe presentations, including perineal gangrene, have been reported.

In practice, the diagnosis of ATD-induced neutropenia is often established through combined clinical and laboratory assessment of a symptomatic patient presenting with fever or pharyngitis, in whom a marked reduction in circulating neutrophils is detected. Key clinical signs include fever ≥38.5°C, erythematous or ulcero-necrotic pharyngitis, stomatitis or gingivitis, and oral ulcerations, which may precede systemic manifestations. Systemic complications such as pneumonia, skin infections, bacteremia, septicemia, or septic shock can develop in advanced cases, highlighting the need for careful clinical vigilance and prompt evaluation in all patients receiving ATDs.

Laboratory, Marrow and Microbiological Findings

ATD-induced neutropenia and agranulocytosis present a distinct hematologic and infectious profile. In the peripheral blood, the hallmark finding is an isolated or predominant reduction of the granulocytic lineage, with preservation of erythroid and megakaryocytic series. Severe neutropenia is defined by an ANC below 500/mm³(<0.5×10⁹/L), and agranulocytosis when ANC falls under 100/mm³ (<0.1×10⁹/L), a threshold associated with a dramatically increased risk of life-threatening infections (Table 2).

Bone marrow examination, though not routinely performed, is valuable in atypical cases or when pancytopenia raises concern for alternative diagnoses such as acute leukemia or myelodysplastic syndromes. The classic finding is selective granulocytic aplasia, with maturation arrest at the promyelocyte or myelocyte stage, while erythroid and megakaryocytic lines remain intact. In some patients, global marrow hypoplasia may be observed, reflecting a broader toxic effect and often correlating with delayed neutrophil recovery and potentially worse prognosis. Detection of anti-granulocyte antibodies can support an immune-mediated mechanism but is not required for diagnosis, as testing is technically challenging, of low specificity, and not routinely recommended.

Profound neutropenia markedly increases susceptibility to infections, particularly from pyogenic bacteria. Gram-positive

Table 2: Laboratory, marrow, and microbiological findings.

Feature	Typical Findings	Clinical/Diagnostic Notes
Peripheral blood	Isolated or predominant neutropenia; absolute neutrophil count (ANC)<1,500/mm³; severe in case of ANC <500/mm³; profound in case of ANC<200/mm³; agranulocytosis in case in ANC<100/mm³	Prompt complete blood count is essential; severity correlates with infection risk
Other cell lines	Usually preserved: erythroid and megakaryocytic series	Pancytopenia suggests broader marrow involvement or alternative diagnosis
Bone marrow	Selective granulocytic aplasia; maturation arrest at promyelocyte/myelocyte stage; preserved erythroid and megakaryocytic lineages	Indicative of classic antithyroid drug-induced agranulocytosis; performed in atypical cases, pancytopenia, or to exclude leukemia/myelodysplastic syndrome
Global marrow hypoplasia	Reduced cellularity of all lineages	May reflect extended toxic effect; often slower neutrophil recovery; potentially worse prognosis
Anti-granulocyte antibodies	May target circulating neutrophils or precursors	Suggests immune-mediated mechanism; low specificity; not routinely tested; absence does not exclude immunologic etiology

Table 3: Prognostic, mortality and key risk factors.

Study / Region	Number of Cases (n)	Mortality	Key Risk Factors	Notes / Interventions
Strasbourg, France (retrospective, 30 cases, 2010–2019)	30	3.3% (1 death)	Severe neutropenia, sepsis	Close monitoring during first 3 months critical
Japan (30-year cohort)	754	4%	Age >60, absolute neutrophil count<100/mm³, infections, comorbidities	High early recognition improves outcomes
Systematic review (international)	Multiple cohorts	21.5% → 5% with G-CSF	Severe neutropenia, delayed treatment	Use of G-CSF significantly reduces mortality
Contemporary optimized management	Various	~2%	Delayed diagnosis, infections	Immediate antithyroid drug withdrawal, antibiotics, G-CSF

organisms such as Streptococcus species and *Staphylococcus aureus*, and Gram-negative bacteria including *Escherichia coli*, Klebsiella species, and *Pseudomonas aeruginosa* are commonly involved. Patients with prolonged neutropenia or immunocompromised status are also at risk of opportunistic fungal infections, mainly *Candida albicans* and *Aspergillus fumigatus*. Comprehensive microbiological assessment — including blood cultures, urine cytobacteriological studies, swabs of pharyngeal or lesion sites, and stool parasitology — is essential from the outset to guide prompt and targeted therapy.

A representative case illustrates the integration of these findings: a 52-year-old man treated with carbimazole for Graves' disease presented with fever and pharyngitis. His ANC was 70/mm^3 (0.07×10^9/L). Bone marrow aspiration revealed selective granulocytic aplasia with maturation arrest at the promyelocyte stage, while erythroid and megakaryocytic lines were preserved. Blood cultures grew *Escherichia coli*, and a throat swab revealed Streptococcus species. Prompt initiation of broad-spectrum antibiotics and G-CSF led to rapid clinical improvement and recovery of neutrophil counts within ten days.

This integrated approach highlights the interplay between hematologic findings, marrow pathology, and infectious risk, emphasizing the critical importance of early recognition, thorough laboratory and microbiological assessment, and timely intervention to reduce morbidity and mortality in patients with ATD-induced neutropenia and agranulocytosis.

Prognosis and Morbidity

The prognosis of severe neutropenia and agranulocytosis induced by ATDs largely depends on the rapidity of diagnosis and the prompt initiation of appropriate treatment (Table 3). In a retrospective series of 30 patients, 43.3% experienced clinical deterioration, with signs of sepsis in 40% and septic shock in 3.3% of cases. These findings underscore the importance of close monitoring, particularly during the first three months of therapy, when the majority of agranulocytosis cases occur.

International data confirm the seriousness of this complication. A Japanese study including 754 cases of ATD-induced agranulocytosis reported 30 deaths, corresponding to a mortality rate of approximately 4%. Risk factors identified included advanced age, severe neutropenia (ANC<100/mm^3), concurrent infections, and pre-existing comorbidities.

Systematic reviews have demonstrated that the use of G-CSF significantly reduces mortality associated with drug-induced agranulocytosis, lowering it from 21.5% to around 5%.

Despite these advances, ATD-induced agranulocytosis remains associated with non-negligible mortality. With optimal management — including immediate discontinuation of the ATD, prompt initiation of antibiotics in the presence of fever or documented infection, and supportive therapy with hematopoietic growth factors — current mortality rates are close to 2%. Delays in diagnosis or treatment, however, can result in severe complications such as systemic infections, pneumonia, or sepsis, substantially increasing the risk of death.

Management: An International Perspective

Management includes immediate discontinuation of ATD, broad-spectrum antibiotics, and G-CSF for severe neutropenia or agranulocytosis [14, 16, 18, 19, 20, 21]. In cases of fever without localizing signs, searching for a deep infectious focus is recommended, typically *via* CT imaging, although iodine contrast may exacerbate hyperthyroidism [16]. Clinicians should consider cross-reactivity between ATDs when planning alternative therapy [16].

Routine WBC monitoring may help detect asymptomatic neutropenia, but idiosyncratic reactions can occur abruptly [12, 22, 23].

The first and most critical step in managing neutropenia induced by synthetic ATDs is the immediate cessation of the offending medication upon clinical suspicion. This is crucial to prevent further deterioration of neutrophil counts and reduce the risk of life-threatening infections. International studies indicate that the onset of agranulocytosis typically occurs within the first three months of treatment, with an incidence estimated between 0.2% and 0.5% among patients receiving ATDs. Early drug discontinuation remains the most consistently recommended intervention across European, American, and Asian clinical guidelines.

Hospitalization in a specialized unit is recommended for patients presenting with profound neutropenia or confirmed agranulocytosis. Protective isolation can be considered to prevent opportunistic infections, particularly in cases of severe neutropenia. However, current evidence suggests that strict isolation may not be mandatory for short-duration neutropenias, such as those induced by ATDs. This nuanced approach is supported by international guidelines, which often balance the risk of infection against the psychological and logistical burden of prolonged isolation.

Some centers, drawing on protocols for chemotherapy-induced neutropenia, advocate for outpatient management in carefully selected patients. Candidates include young, otherwise healthy individuals, asymptomatic at presentation, and residing near a healthcare facility capable of rapid intervention. Outpatient care may be extended to patients presenting with mild febrile episodes, if close medical monitoring and rapid access to hospital care are ensured. Studies from Europe and Japan have reported successful outpatient management in selected ATD-induced neutropenia cases, highlighting the importance of individualized care.

Prompt initiation of broad-spectrum empirical antibiotics is essential, particularly given the increased risk of infections by

multidrug-resistant organisms. A comprehensive microbiological assessment should accompany antibiotic therapy to guide targeted treatment if pathogens are identified. International clinical guidelines recommend early intervention, as delayed antibiotic administration is strongly associated with higher morbidity and mortality in ATD-induced neutropenia.

In cases of "naked fever" (fever without localizing signs), the search for a deep infectious focus is mandatory. Computed Tomography (CT) imaging is generally recommended to identify hidden infections; however, its use can be challenging in patients with hyperthyroidism due to the required iodine contrast, which may exacerbate thyroid dysfunction.

The use of G-CSF can be considered, although its efficacy is not uniformly established. G-CSF is particularly indicated in elderly patients, those with multiple comorbidities (including chronic kidney disease), patients with severe infections, or an ANC below 100 cells/mm^3 (<0.1×10^9/L). International studies suggest that G-CSF accelerates neutrophil recovery and may reduce hospital stay, though its routine use is still debated.

In cases where ATD discontinuation leads to thyroid hormone imbalance, temporary levothyroxine replacement can be administered to maintain euthyroidism. This approach is particularly useful as a bridge while planning definitive therapy such as thyroidectomy or radioactive iodine treatment. Maintaining thyroid function during the neutropenic period helps prevent additional systemic stress and complications.

All cases of ATD-induced neutropenia should be systematically reported to national and international pharmacovigilance authorities, even when the association is well documented. Reporting contributes to ongoing surveillance, enhances understanding of risk factors, and informs updates to treatment guidelines. The World Health Organization (WHO) and regulatory agencies across Europe, the United States, and Asia strongly emphasize this practice to improve patient safety globally.

Table 1 summarizes international recommendations for the management of ATD–induced neutropenia and agranulocytosis, including monitoring strategies, early recognition, and therapeutic interventions such as drug discontinuation, infection prophylaxis, and use of G-CSF (Table 1).

Cross-Allergy Between Synthetic Antithyroid Drugs: A Major Clinical Challenge

Cross-allergy between synthetic ATDs represents a significant clinical concern in the management of hyperthyroidism, particularly in cases of severe immuno-allergic reactions such as agranulocytosis. Although Propylthiouracil (PTU) and carbimazole (or its active metabolite, methimazole) belong to chemically distinct families — thio-uracils and imidazoles, respectively — cases of cross-allergy have been reported, suggesting the potential for immunologic cross-reactivity. This susceptibility may be mediated by shared immunological mechanisms, including T-cell recognition or antibody production directed against structurally similar epitopes.

In practice, the occurrence of agranulocytosis under carbimazole generally contraindicates subsequent use of PTU, and *vice versa*, due to the potentially fatal risk of recurrence. This caution is particularly warranted because the onset of such reactions is often early, and relapse upon re-exposure can occur more rapidly and may be more severe. International reports indicate cross-allergy rates ranging from 15% to 50%, depending on the initial manifestation and method of therapeutic reintroduction.

Consequently, the safest strategy often involves permanent discontinuation of all ATDs and the use of definitive alternative therapies, such as thyroidectomy or, in selected cases, radioactive iodine therapy under strict endocrinological supervision.

It is crucial to distinguish benign adverse effects — such as cutaneous rash, arthralgias, or pruritus — from severe reactions like profound neutropenia or agranulocytosis, as management strategies differ substantially. For moderate manifestations, switching to an alternative ATD may be considered under close monitoring, although this remains high-risk.

A multidisciplinary discussion involving an internist, hematologist, endocrinologist, and clinical pharmacologist is often necessary to evaluate the benefit-risk ratio of a potential therapeutic switch. Such collaborative evaluation is emphasized in international guidelines to ensure patient safety while optimizing hyperthyroidism management (Table 4).

Prevention and Monitoring Strategies

Patient education is the cornerstone of preventing severe complications associated with ATD therapy (Table 5). Every patient receiving ATDs should be thoroughly informed about the early warning signs of neutropenia, including fever, sore throat, and oral ulcers. They should be encouraged to seek immediate medical attention if any of these symptoms appear. International guidelines consistently emphasize that timely recognition and reporting of symptoms can significantly reduce morbidity and mortality associated with ATD-induced neutropenia.

Given the potential severity of neutropenia and agranulocytosis, regular monitoring of neutrophil counts is recommended, particularly during the first three months of treatment, which is when most cases occur. This recommendation is incorporated into the product labeling

Table 4: Cross-reactivity between synthetic antithyroid drugs and recommended management.

Aspect	Observation / Recommendation	International Data / Guidelines
Chemical families	Propylthiouracil: thio-uracils; Carbimazole/Methimazole: imidazoles	Chemically distinct, but potential immunological cross-reactivity exists
Cross-allergy incidence	15-50% depending on initial reaction and reintroduction method	Reported in Europe, US, Japan (case series and registry data)
Severe reactions	Agranulocytosis under one anti-thyroid drug contraindicates use of the other	International societies recommend permanent discontinuation
Mild/Moderate reactions	Rash, arthralgia, pruritus may allow cautious switch under close supervision	Multidisciplinary monitoring required; risk of severe recurrence remains
Definitive therapy	Thyroidectomy or radioactive iodine therapy	International guidelines endorse as safest alternative after severe allergic reaction
Multidisciplinary approach	Internist, hematologist, endocrinologist, pharmacologist	Ensures benefit-risk assessment, optimal patient safety

Table 5: Prevention and monitoring strategies.

Aspect	Recommendation	International guidelines / Data
Patient education	Recognize fever, sore throat, oral ulcers	Emphasized by ATA, ETA, JTA
Initial laboratory monitoring	Baseline complete blood count; monitor first 3 months	Majority of cases occur early
Routine complete blood count screening	Optional: weeks 2-6	Debate exists; sudden onset limits effectiveness
Rapid response	Immediate consultation upon symptoms	Most effective globally
Documentation	Follow antithyroid drug labeling	Internationally recommended

Table 6: Predictive strategies and personalized medicine approaches.

Predictive approach	Description / Application	Potential / International Relevance
Pharmacogenetics	HLA allele profiling	Improves risk stratification; Europe, Asia, US
Omics approaches	Metabolomics, transcriptomics, proteomics	Identify predictive biomarkers; research stage
Artificial Intelligence (AI)	Machine learning on Electronic Health Record (HER)	Detects subtle signals, alerts clinicians
Integrated models	Clinical+biological+pharmacogenetic+behavioral data	Enables individualized predictive models
Personalized prescribing	Tailored antithyroid drug therapy	Reduces severe complications, improves safety

of commonly used ATDs, including methimazole, carbimazole, and PTU. Early detection through vigilant monitoring allows for rapid intervention, improving patient outcomes.

Systematic laboratory surveillance, however, remains a subject of debate. Some clinical teams advocate for a CBC between the second and sixth week of therapy. Yet, the sudden onset of agranulocytosis can limit the effectiveness of scheduled screening. Consequently, therapeutic education and rapid diagnostic responsiveness are considered the most effective strategies for preventing severe complications.

Predictive Perspectives and Personalized Medicine

In the context of personalized medicine, several strategies are being explored to predict the occurrence of drug-induced agranulocytosis. Pharmacogenetic approaches, particularly the study of Human Leukocyte Antigen (HLA) alleles, have shown promise in identifying patients at higher risk (Table 6). Specific HLA genotypes have been associated with an increased susceptibility to antithyroid drug-induced agranulocytosis, allowing for targeted monitoring and risk mitigation.

Additionally, analyses of metabolic, transcriptomic, and proteomic profiles may, in the future, further refine risk stratification by identifying biological signatures predictive of adverse reactions.

Artificial Intelligence (AI) represents a promising tool for enhancing the prediction of drug-related complications. By leveraging data from electronic medical records, machine-learning algorithms can detect subtle warning signals, identify high-risk patient profiles, and generate early alerts for potential adverse events. Early studies have demonstrated that integrating clinical, laboratory, and pharmacogenetic data improves predictive accuracy and supports proactive clinical decision-making.

The aggregation of clinical, biological, pharmacogenetic, and behavioral data could soon enable the construction of individualized predictive models. Such models are central to the ongoing digital transformation of medicine, which emphasizes tailored prescribing and personalized risk management. These approaches aim not only to prevent severe complications such as agranulocytosis but also to optimize therapeutic efficacy and patient safety.

Conclusions

ATD-induced neutropenia and agranulocytosis represent rare but serious complications of hyperthyroidism treatment, with an estimated incidence ranging from 0.1% to 0.5% worldwide. Epidemiological data indicate that most cases occur within the first three months of therapy, highlighting the critical period for clinical vigilance. Clinically, patients typically present with fever, sore throat, and mucosal ulcers, although severe infections such as sepsis, bacteremia, or pneumonia may also develop. Biologically, agranulocytosis is defined by an ANC below 500/μL, with counts below 100/μL conferring the highest risk of life-threatening infections.

Effective management requires immediate discontinuation of the offending ATD, supportive care with hospitalization or carefully monitored outpatient management, and initiation of broad-spectrum empirical antibiotics (Figure 1). The use of G-CSF can accelerate

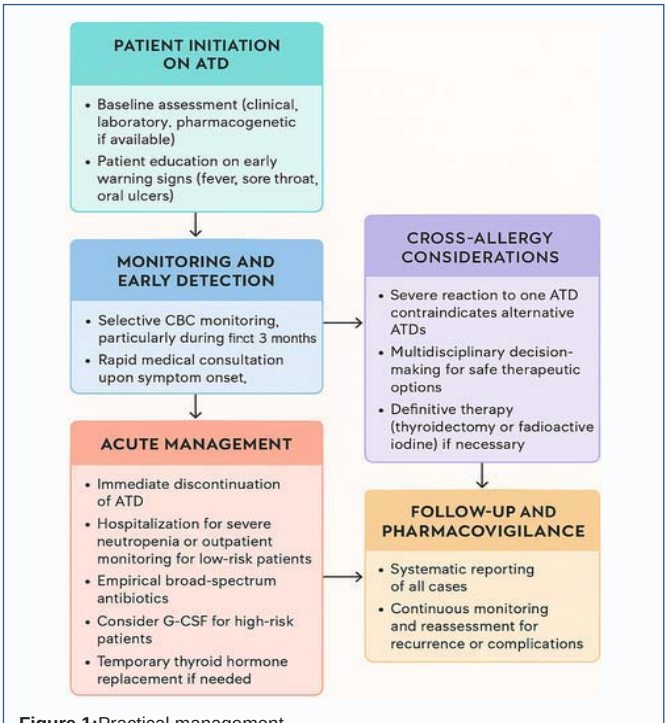


Figure 1: Practical management.

neutrophil recovery in high-risk patients, particularly the elderly, those with comorbidities, or those with severe infections. Temporary thyroid hormone replacement may be used to maintain euthyroidism during the acute period.

Cross-allergy between synthetic ATDs remains a significant clinical challenge, with reported rates between 15% and 50%. Severe immuno-allergic reactions generally contraindicate re-exposure, necessitating definitive therapies such as thyroidectomy or radioactive iodine. Prevention relies on patient education regarding early symptoms, selective laboratory monitoring, and rapid diagnostic response rather than routine screening, given the often-abrupt onset of neutropenia.

Emerging predictive and personalized medicine strategies, including HLA pharmacogenetic profiling, omics analyses, and AI-based risk modeling, offer the potential to identify high-risk patients before adverse events occur. Integration of clinical, biological, and pharmacogenetic data may allow individualized therapeutic decisions, reducing the incidence of severe complications while optimizing treatment efficacy.

Overall, a comprehensive approach that combines epidemiological awareness, early clinical recognition, biological monitoring, multidisciplinary collaboration, and personalized predictive strategies is essential to minimize morbidity and mortality associated with ATD therapy. These measures not only improve patient safety but also advance the precision and effectiveness of hyperthyroidism management on a global scale.

Conflict of Interest Statement

The authors report no financial or personal relationships that could inappropriately influence the content of this article.

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