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Advances and Future Directions in Drug-Induced Agranulocytosis Care for Geriatric Patients

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Abstract

Idiosyncratic drug-induced agranulocytosis is a rare but potentially fatal adverse drug reaction characterized by a sudden and profound drop in neutrophil count, predisposing patients to severe infections. Although its overall incidence is low, the condition poses a significant clinical challenge, particularly among older, frail individuals with multiple comorbidities and high levels of polypharmacy. In this vulnerable population, the unpredictable onset and wide spectrum of causative medications further complicate management. Traditional strategies focus on early recognition and prompt discontinuation of the offending drug, but preventive measures have historically been limited. Recent advances in pharmacogenomics have shed light on individual susceptibility, with specific HLA alleles and genetic polymorphisms identified as key risk factors. The integration of genetic, demographic, and clinical characteristics into defined risk clusters supports a more personalized prevention strategy. Moreover, the application of big data analytics and artificial intelligence (AI) holds promise for predictive modeling, real-time signal detection, and improved pharmacovigilance. Technological innovations - such as telemedicine, wearable sensors, and home-based neutrophil monitoring - can facilitate earlier detection and targeted intervention, particularly in geriatric patients at higher risk. Therapeutic patient education (TPE) is essential in raising awareness, reinforcing adherence to monitoring protocols, and empowering older adults in self-care. This review explores how the convergence of scientific, clinical, and technological advances is reshaping the management of idiosyncratic drug - induced agranulocytosis, paving the way toward a more proactive, preventive, and individualized approach - especially relevant in the context of aging populations.

Keywords: Drug-induced agranulocytosis; Elderly patients; Frailty patients; Polypharmacie; Multiples comorbidities; Risk clusters; Big data, Artificial intelligence; Telemedicine; Connected sensors; Therapeutic patient education; Prevention, Prediction

Introduction

Idiosyncratic drug-induced agranulocytosis (IDIA) is a rare but potentially life-threatening adverse drug reaction characterized by a profound reduction in neutrophil count, frequently leading to severe infections and, in some cases, death [1,2]. Although uncommon, IDIA remains a major concern in internal and geriatric medicine due to its unpredictable onset, the large variety of implicated drugs, and the lack of reliable early warning signs. This condition is particularly worrisome in older adults, who often present with frailty, multiple chronic comorbidities, and polypharmacy - all of which can increase susceptibility to adverse drug reactions and delay recognition of evolving neutropenia. While certain medications - such as antithyroid drugs, clozapine, sulfonamides, and some antibiotics - are more frequently associated with IDIA, the idiosyncratic nature of the reaction reflects a multifactorial etiology. This includes genetic predispositions (e.g., HLA variants), immune-mediated mechanisms, and interactions with existing health conditions and complex drug regimens [1,2].

Despite its rarity, IDIA carries high morbidity and a risk of rapid clinical deterioration, particularly in older and vulnerable patients, often requiring immediate drug withdrawal and urgent supportive interventions upon diagnosis [3]. However, early

identification remains challenging due to the delayed onset and non-specific initial symptoms. In recent years, advances in pharmacogenomics have begun to elucidate individual susceptibility factors, while the emergence of big data analytics and artificial intelligence (AI) offers new possibilities for predictive modeling and real-time pharmacovigilance. Additionally, the integration of telemedicine, wearable technologies, and home-based blood monitoring opens new perspectives for earlier detection and intervention, especially in geriatric patients with limited mobility or complex care needs [3,4].

This review aims to provide a comprehensive and updated overview of current knowledge and evolving approaches to IDIA, with a particular focus on aging populations [5,6]. It underscores how technological and scientific innovations - combined with a patient-centered, multidisciplinary care model - can support improved risk stratification, early detection, and more personalized prevention and management strategies in internal and geriatric medicine.

Idiosyncratic Drug-Induced Agranulocytosis

Idiosyncratic drug-induced cytopenias result from a decrease in blood cell counts - affecting red blood cells (anemia), neutrophils (neutropenia), platelets (thrombocytopenia), or even multiple hematopoietic lineages, as in drug-induced thrombotic microangiopathy. These hematological abnormalities arise from unpredictable reactions to drugs, unrelated to dosage or known pharmacological properties (Table 1). Their occurrence poses a particular concern in older adults, who often present with polypharmacy, reduced physiological reserves, and multiple comorbidities that may amplify susceptibility and obscure early clinical signs.

Table 1: Definition and pathophysiology of idiosyncratic drug-induced cytopenias [4-9].

Aspect	Description
Definition	Reduction in the number of blood cells (red blood cells, neutrophils or platelets) due to an unpredictable reaction to a drug, unrelated to the dose or pharmacological properties of the drug
Physiopathology	The exact mechanisms are often poorly understood, but may include: - Immunological reactions: The drug or its metabolites may modify cellular antigens, resulting in an immune response against blood cells - Direct toxicity: some drugs can have a direct toxic effect on hematopoietic cells or bone marrow - Genetic predisposition: individual genetic variations may make some people more susceptible to developing cytopenias in response to certain drugs

Neutropenia, defined by an abnormally low number of neutrophils - key cells in the defense against bacterial and fungal infections - is typically classified by severity: mild (1000–1500 cells/μL or 1–1.5 × 10^9/L), moderate (500-1000 cells/μL or 0.5-1 × 10^9/L), and severe (<500 cells/μL or <0.5 × 10^9/L). The risk of infection increases significantly as neutrophil counts fall, especially in frail, immunocompromised, or malnourished older patients [7]. Agranulocytosis represents a particularly severe and often abrupt form of neutropenia, defined by neutrophil counts below 500 cells/μL - and in many cases below 100 cells/μL (0.1 × 10^9/L) - leading to a critically compromised innate immune defense [3].

Idiosyncratic drug-induced agranulocytosis (IDIA) is a rare but severe form of neutropenia, occurring at an estimated incidence of 6-10 cases per million inhabitants per year [1,2]. It is caused by an adverse drug reaction driven by individual-specific factors such as genetic predisposition (e.g., HLA alleles), immune dysregulation, or other poorly understood mechanisms. Unlike general neutropenia, IDIA often results from bone marrow suppression and is not dose-dependent, rendering prediction and prevention particularly challenging - especially in geriatric patients frequently exposed to high-risk drugs due to complex therapeutic regimens.

In older, frail, or multimorbid individuals, the consequences of IDIA may be particularly severe, including prolonged hospitalization, sepsis, and death. A mortality rate between 5% and 20% has been reported for severe drug-induced neutropenia and agranulocytosis [8]. Prompt recognition, early discontinuation of the causative agent, and rapid initiation of supportive therapy - including empirical antibiotics and hematopoietic growth factors - are essential to prevent irreversible complications [9]. In this context, systematic vigilance is required, particularly in elderly patients receiving high-risk medications in the setting of polypharmacy and impaired homeostatic reserves.

IDIA can be triggered by a wide and diverse range of medications, reflecting the unpredictable and multifactorial nature of this adverse drug reaction. Historically, well-established culprit drugs include certain antimicrobials (e.g., trimethoprim-sulfamethoxazole, some cephalosporins), non-steroidal anti-inflammatory drugs (NSAIDs) such as phenylbutazone (with a lower incidence among newer NSAIDs), antithyroid agents (e.g., methimazole, propylthiouracil), and the antipsychotic clozapine, which is associated with a particularly high risk of agranulocytosis and is subject to mandatory hematological monitoring in many countries [10,11].

Other commonly implicated pharmacological classes include anticonvulsants (e.g., carbamazepine), antiarrhythmics (e.g., procainamide), and certain chemotherapeutic agents. While the latter typically cause predictable, dose-dependent myelosuppression, they may also, in rare cases, precipitate idiosyncratic agranulocytosis [12,13]. Emerging therapeutic modalities - such as monoclonal antibodies, targeted biologics, and even advanced

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cell- and gene-based therapies (including CAR T-cell therapy) - have also been associated with isolated cases of severe neutropenia or agranulocytosis, further expanding the landscape of concern [14,15].

This diversity in causative agents is especially relevant in geriatric medicine. Older adults are more likely to be exposed to multiple high-risk drugs due to polymorbidity and complex therapeutic regimens. They are also more vulnerable to adverse outcomes due to age-related changes in drug metabolism, diminished bone marrow reserve, and impaired immune responses. In this context, careful medication history taking, comprehensive risk-benefit analysis, and systematic pharmacovigilance are essential. Moreover, as the list of potentially offending drugs continues to evolve, clinicians must remain vigilant for newly implicated agents, particularly in polymedicated, frail older patients [16,17].

Understanding Risk: The Concept of Risk Clusters

The traditional approach to drug-induced agranulocytosis has primarily centered on identifying individual high-risk drugs. While this drug-specific perspective remains clinically useful, it fails to account for the multifactorial nature of susceptibility to idiosyncratic drug-induced agranulocytosis (IDIA). In clinical practice - especially in older and frail patients - a more nuanced approach is needed. This has led to the concept of "risk clusters", which refer to combinations of genetic, demographic, clinical, and pharmacological factors that together increase the likelihood of developing IDIA.

Several key components have been identified within these risk clusters:

a) Genetic Predisposition: Certain HLA alleles and polymorphisms in genes involved in immune regulation and drug metabolism have emerged as important susceptibility factors [18,19]. Variants in genes encoding drug-metabolizing enzymes (e.g., CYPs, NATs) or immune regulators (e.g., HLA-B, HLA-DR alleles) can predispose individuals to aberrant immune responses following drug exposure. Genetic screening, although not yet standard practice, may help identify high-risk individuals - particularly in the context of geriatric patients receiving high-risk drugs.

b) Age and Sex: Advanced age and female sex are both recognized as risk factors for IDIA, particularly with drugs like antithyroid agents and clozapine [20,21]. Age-related changes in pharmacokinetics - such as reduced renal or hepatic clearance - can result in elevated drug levels in older adults, while immunosenescence and inflammaging may alter immune reactivity. In addition, hormonal and immune differences in females may contribute to increased susceptibility. These factors are particularly relevant in elderly women with multimorbidity and altered drug handling capacity.

c) Comorbidities: Chronic conditions such as autoimmune diseases, chronic infections, hepatic insufficiency, and renal impairment can increase the risk of IDIA [22]. Autoimmune diseases often entail baseline immune dysregulation, while hepatic and renal dysfunction can impair drug clearance, contributing to drug accumulation and heightened immunogenicity. In geriatric patients, such comorbidities are common and often co-exist, compounding the risk.

d) Polypharmacy and Drug–Drug Interactions: Polypharmacy - highly prevalent in older adults-significantly increases the complexity of pharmacological management and the risk of drug interactions [23,24]. Concomitant use of immunomodulatory agents, myelotoxic drugs, or inhibitors of drug metabolism can potentiate bone marrow suppression. Some combinations may have synergistic effects on hematopoietic toxicity, while others may mask or delay the recognition of agranulocytosis, complicating timely intervention.

e) History of Previous Idiosyncratic Drug Reactions: A prior history of idiosyncratic or immune-mediated adverse drug reactions is a significant risk marker for subsequent reactions, including IDIA [25]. In elderly patients with extensive therapeutic histories, cumulative immune sensitization or previous exposure to structurally similar agents may prime the immune system for exaggerated responses.

Identifying these risk clusters through comprehensive data integration - combining electronic health records, genetic data, and pharmacological profiles - is crucial for improving predictive accuracy and tailoring preventive strategies (Table 2) [18-25]. In older and multimorbid patients, where clinical complexity is high, this approach may allow for personalized risk stratification, informed consent, preemptive monitoring protocols, and judicious therapeutic decisions. Ultimately, a shift from reactive to proactive and individualized risk management in IDIA - especially in geriatric medicine - offers the promise of reducing morbidity, hospitalizations, and mortality associated with this rare but serious adverse drug reaction.

Table 2: Risk Clusters for Idiosyncratic Drug-Induced Agranulocytosis (IDIA) in Older Adults [18-25].

Risk Factor Category	Specific Elements	Relevance in Older Adults
Genetic Predisposition	- HLA alleles (e.g., HLA-B38, HLA-DRB108) - Polymorphisms in CYP, NAT, or ABC transporter genes	- Underexplored in geriatrics but increasingly accessible - May guide personalized prevention in high-risk individuals
Age and Sex	- Age > 65 years - Female sex	- Age-related changes in drug clearance - Immunosenescence and altered immune reactivity
Comorbidities	- Autoimmune diseases - Chronic infections - Hepatic or renal dysfunction	- Common in older adults - Increase vulnerability to immune dysregulation and drug accumulation

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Polypharmacy & Drug Interactions	- ≥5 concurrent medications - Use of myelotoxic or immunomodulatory agents	- Frequent in geriatric care - Increases risk of synergistic hematological toxicity and delayed recognition
Prior History of ADRs	- Previous idiosyncratic or immune-mediated drug reactions	- Indicative of heightened immune sensitivity - May reflect cumulative immunological priming
Frailty and Functional Status	- Poor nutritional status - Cognitive or physical decline	- May delay symptom recognition - Limits adherence to monitoring protocols
Healthcare Access and Monitoring	- Lack of regular follow-up - Home-based care settings	- May impede early detection and timely drug discontinuation

The Power of Big Data and Artificial Intelligence

The vast amounts of health-related data generated from electronic health records (EHRs), pharmacovigilance databases, genomic research, and even non-traditional sources such as social media present unprecedented opportunities to understand and manage the complexities of idiosyncratic drug-induced agranulocytosis (IDIA). The integration of big data analytics and artificial intelligence (AI) holds particular promise in the field of geriatric medicine, where the burden of multimorbidity, polypharmacy, and altered pharmacokinetics creates significant challenges in risk prediction and clinical decision-making.

AI-enhanced data analysis enables a paradigm shift from retrospective recognition of adverse drug reactions toward prospective risk modeling, personalized monitoring, and preventive strategies tailored to older, frail, and vulnerable populations.

Key Applications of Big Data and AI in Managing IDIA Risk in Older Adults:

a) Identification of Novel Risk Factors and Drug Interactions: Machine-learning techniques can analyze high-dimensional data from EHRs, genomic studies, and real-world pharmacovigilance platforms to uncover new and complex associations. In older adults with multiple comorbidities and extensive drug exposure histories, these tools can help identify unexpected drug-drug interactions or cumulative toxicities associated with agranulocytosis risk [26,27]. AI may also detect genetic markers or immunological profiles that confer increased susceptibility in elderly patients who may otherwise be overlooked using standard assessment models.

b) Development of Predictive Models for Risk Stratification: AI algorithms trained on large datasets can generate predictive models that estimate an individual's likelihood of developing IDIA based on integrated variables such as age, sex, renal/hepatic function, genetic polymorphisms, comorbidities, and pharmacological exposure [27,28]. In older patients - who often accumulate multiple risk factors-these models can guide pre-emptive risk stratification prior to initiating high-risk medications (e.g., antithyroid drugs, clozapine), facilitating safer prescribing practices.

c) Enhanced Signal Detection in Pharmacovigilance: Traditional pharmacovigilance systems may miss subtle or delayed-onset signals, particularly in the elderly, where symptoms of agranulocytosis can be nonspecific or attributed to underlying frailty. AI can improve the sensitivity and specificity of signal detection by analyzing a wide array of structured and unstructured data - including patient reports, registry data, and even public sources like social media - for early signs of drug-associated neutropenia [29,30]. Early signal recognition is especially valuable in geriatric patients, where delayed intervention may result in rapid clinical deterioration.

d) Personalized Risk Assessment and Clinical Decision Support: Perhaps the most transformative contribution of AI lies in its ability to integrate heterogeneous data sources to deliver patient-specific risk assessments [31,32]. For older patients, such tools can combine clinical parameters (e.g., frailty index, organ function, medication burden), pharmacogenomic data, and social determinants (e.g., care setting, support network) to tailor monitoring intensity and therapeutic strategies. This individualized approach is particularly relevant in geriatrics, where interindividual variability is high and "one-size-fits-all" guidelines are often inadequate.

By leveraging these tools, clinicians can move toward a proactive and data-driven approach to IDIA management - especially in older populations disproportionately affected by this complication. The integration of AI into clinical workflows also opens avenues for real-time clinical decision support, alerting prescribers to elevated risks based on a patient's evolving profile.

As these technologies mature, they are poised to redefine pharmacovigilance and personalized medicine for IDIA, contributing to safer prescribing, earlier detection, and improved outcomes for high-risk groups, including frail older adults with complex medication regimens [33] (Table 3).

Table 3: Applications of Big Data and Artificial Intelligence (AI) in Preventing and Managing Idiosyncratic Drug-Induced Agranulocytosis (IDIA) in Older Adults [26-33].

Application Area	Description	Specific Relevance in Geriatric Patients
1. Risk Factor Discovery	Identification of novel genetic, clinical, and pharmacological risk factors using machine learning	Detects hidden or complex patterns in older adults with multimorbidity and polypharmacy
2. Predictive Modeling	Development of individual risk scores integrating age, sex, comorbidities, genetics, and medications.	Enables pre-treatment stratification in elderly patients before initiating high-risk drugs

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3. Enhanced Pharmacovigilance Signal Detection	AI-based analysis of real-world data (EHRs, registries, spontaneous reports, social media)	Allows early detection of agranulocytosis in polymedicated older adults with nonspecific or delayed symptoms
4. Clinical Decision Support Systems (CDSS)	Integration of AI tools into prescribing platforms and EHRs for real-time alerts	Alerts clinicians to high-risk drug combinations or vulnerable patient profiles at the point of care.
5. Personalized Monitoring Strategies	Adaptive follow-up intensity based on individualized risk assessment models	Reduces unnecessary interventions while improving early detection in frail or home-bound elderly patients
6. Integration of Genomic Data	Use of pharmacogenomic testing to tailor drug selection	Guides safer prescribing in elderly individuals with altered drug metabolism or immune response pathways
7. Multisource Data Fusion	Cross-analysis of clinical, biological, pharmacological, and social data	Provides a holistic view of older patients' risks, including non-clinical factors (e.g., care setting, isolation)

Innovations in Biological Understanding

Recent advancements in biology are providing deeper insights into the complex mechanisms underlying drug-induced agranulocytosis (IDIA), insights that are particularly relevant for improving prevention, diagnosis, and treatment in older, frail patients. These innovations hold promise for tailoring safer therapeutic approaches in populations with increased vulnerability due to age-related immune changes, comorbidities, and polypharmacy.

a) Pharmacogenomics: Ongoing research into genetic markers associated with susceptibility to IDIA continues to refine our understanding of individual risk profiles [34,35]. In geriatric populations, where physiological heterogeneity is high, the integration of pharmacogenomic testing prior to initiating high-risk medications may enable personalized prescribing strategies that minimize adverse effects and optimize efficacy.

b) Immunopathogenesis: Investigations into immune mechanisms involved in IDIA - such as drug-dependent antibody formation and cytotoxic T cell activation against neutrophils - are critical for developing targeted therapies [35,36]. Older adults often exhibit altered immune regulation (immunosenescence) that may modify these pathogenic processes, underscoring the need for age-adapted therapeutic interventions that modulate harmful immune responses while preserving immune competence.

c) Neutrophil Biology: Breakthroughs in understanding neutrophil development, survival, and clearance mechanisms offer new therapeutic avenues [37,38]. In elderly patients, where bone marrow reserves and neutrophil regenerative capacity may be impaired, these insights could inform novel treatments aimed at accelerating recovery from neutropenia and reducing infection-related morbidity.

d) Biomarkers: The identification of early biomarkers predictive of impending agranulocytosis is a major goal for proactive monitoring and timely intervention [39,40]. For older and frail patients, sensitive and specific biomarkers detectable in peripheral blood or bone marrow could transform clinical management by enabling earlier diagnosis and reducing the risk of severe infectious complications through prompt treatment adjustments.

Together, these biological innovations are essential for advancing our understanding of IDIA and for developing more effective, personalized strategies to prevent and manage this serious adverse drug reaction - particularly in aging populations at heightened risk due to complex clinical profiles [41].

Integrating Telemedicine and Connected Sensors for Enhanced Monitoring

Telemedicine and connected sensors represent promising innovations for enhancing patient monitoring, particularly in the early detection phase of drug-induced agranulocytosis (IDIA). These technologies facilitate more proactive and personalized care, which is especially crucial for older adults who may have limited mobility, cognitive challenges, or difficulties accessing frequent in-person medical evaluations.

a) Remote Symptom Monitoring: Telehealth platforms enable elderly patients to report symptoms such as fever, fatigue, or sore throat-early indicators of infection and potential complications of agranulocytosis-from their homes [42,43]. Regular, remote symptom tracking supports earlier identification of concerning clinical changes and allows healthcare providers to intervene more swiftly, a critical advantage for frail older adults at higher risk of rapid deterioration.

b) Wearable Sensors: Continuous monitoring devices measuring vital signs (e.g., body temperature, heart rate, oxygen saturation) provide an additional safety net for at-risk patients [44,45]. These sensors can automatically alert healthcare professionals to abnormal trends, enabling timely clinical reassessment. This real-time data stream is particularly beneficial for elderly patients, in whom subtle physiological changes might otherwise go unnoticed until more severe illness develops.

c) Home-Based Blood Cell Counts: Emerging point-of-care testing (POCT) technologies for home monitoring of white blood cell (WBC) counts, especially neutrophils, offer a transformative tool for managing IDIA risk [46,47]. Designed for ease of use and reliability, these devices allow high-risk older patients - such as those newly prescribed agranulocytosis-associated drugs or those within identified risk clusters - to perform frequent blood count checks without clinic visits. Early detection of neutropenia in the home setting can drastically reduce time to diagnosis and initiation of treatment, thereby preventing severe infectious complications.

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In summary, the integration of telemedicine and connected health technologies into routine care pathways can markedly strengthen early monitoring and management of IDIA [48,49]. These tools promote a shift toward patient-centered, accessible care tailored to the needs of elderly and frail patients, ultimately enabling earlier diagnosis, prompt treatment, and improved clinical outcomes (Table 4).

Table 4: Telemedicine and Connected Health Technologies for Early Detection and Management of drug-induced agranulocytosis (DIA) in Older Adults [42-49].

Technology	Description	Benefits and Specific Relevance in Older Adults
Remote Symptom Monitoring	Platforms enabling patients to report symptoms (fever, fatigue, sore throat) remotely and regularly	Facilitates early recognition of infection symptoms without requiring clinic visits; crucial for mobility-limited or homebound elderly
Wearable Sensors	Devices continuously tracking vital signs (body temperature, heart rate, oxygen saturation) with automated alerts	Detects early physiological changes; helps overcome atypical symptom presentation in frail older adults
Home-Based Blood Cell Counts	Point-of-care testing devices allowing patients to measure WBC/neutrophil counts at home	Enables frequent monitoring without travel; accelerates diagnosis and treatment in high-risk, polymedicated elderly patients

The Crucial Role of Therapeutic Patient Education

Therapeutic patient education (TPE) plays a pivotal role in reducing the risks associated with idiosyncratic drug-induced agranulocytosis (IDIA), especially among older adults who may be more vulnerable due to multimorbidity, cognitive decline, or complex medication regimens. By equipping patients with relevant knowledge and self-management tools, TPE promotes safer medication use, enhances early symptom recognition, and facilitates timely medical intervention - key factors for preventing severe complications in this high-risk population.

a) Medication Awareness: A core objective of TPE is to ensure that patients fully understand the medications they take, particularly those with a known risk of IDIA [50,51]. For elderly patients, this involves clear communication about potential side effects, including agranulocytosis, and the critical importance of promptly reporting any early symptoms such as fever, sore throat, or oral ulcers, which may signal neutropenia or infection.

b) Early Symptom Recognition: TPE empowers older adults and their caregivers to identify early clinical signs of agranulocytosis. Given that older patients may present atypically or have diminished symptom perception, education about warning signs increases the likelihood of timely medical consultation, improving chances of early diagnosis and recovery [52,53].

c) Adherence to Monitoring Protocols: Regular blood monitoring is essential for patients on high-risk medications. TPE can improve adherence to scheduled white blood cell (WBC) counts and clinical follow-ups by clarifying the rationale behind testing and highlighting the risks of missed appointments [54,55]. This is particularly important in geriatrics, where cognitive or logistical barriers may impair compliance.

d) Self-Management Strategies: TPE supports infection prevention through teaching effective hygiene practices, avoidance of high-risk environments during neutropenia, and vigilance for infection signs [56]. These behaviors are crucial in older adults who face increased infectious risks and complications from agranulocytosis.

Tailored TPE programs delivered via digital platforms and mobile applications further enhance patient engagement and retention of critical information [57,58]. Such tools can be adapted to individual literacy levels, cognitive capacities, and risk profiles, offering features like symptom trackers, medication reminders, educational videos, and direct communication with healthcare providers. This interactive, patient-centered approach can significantly improve the management of IDIA in elderly populations.

In summary, therapeutic patient education is a cornerstone of preventive care for IDIA [59]. By fostering medication awareness, early symptom detection, adherence to monitoring, and proactive self-care behaviors, TPE enhances safety and clinical outcomes - particularly for older, frail patients at elevated risk of this serious adverse drug reaction.

Prevention and Prediction: Towards a Proactive Approach

The ultimate goal in managing idiosyncratic drug-induced agranulocytosis (IDIA) is its prevention, especially critical in older adults who face heightened vulnerability due to multimorbidity, polypharmacy, and physiological changes. Achieving effective prevention demands a comprehensive, multifaceted strategy that combines clinical vigilance, technological innovation, and patient and public engagement.

Key Components of a Preventive Strategy for IDIA in Older Adults:

a) Evidence-Based Prescribing: Clinicians must carefully assess the risk-benefit balance of medications known to carry IDIA risk, particularly in elderly patients with complex health profiles [60,61]. For those identified as high risk through genetic, clinical, or pharmacological factors, safer therapeutic alternatives should be prioritized. This cautious approach is essential to minimize preventable cases of agranulocytosis in frail populations.

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b) Targeted Monitoring Strategies: Prevention relies on risk-stratified monitoring protocols customized to individual patient risk clusters. In older adults, this often involves more frequent blood count surveillance, enhanced by telemedicine and connected sensor technologies that allow remote symptom and vital sign monitoring [62,63]. Such innovations enable earlier detection of neutropenia and timely clinical intervention, mitigating severe complications.

c) Pre-prescription Risk Assessment: Artificial intelligence-powered predictive models are transformative tools for prevention. By integrating genetic data, comorbidities, medication histories, and other relevant factors, these models can estimate an individual's IDIA risk prior to therapy initiation [64,65]. This facilitates personalized prescribing and monitoring plans, reducing adverse drug reaction incidence among elderly patients.

d) Pharmacovigilance Enhancement: Strengthening pharmacovigilance systems is critical for real-time identification and evaluation of IDIA cases. The incorporation of big data analytics and AI improves signal detection sensitivity, allowing earlier recognition of emerging drug safety concerns and enabling prompt regulatory responses [66,67]. Enhanced reporting mechanisms support a more precise understanding of IDIA epidemiology and risk factors in geriatric populations.

e) Public Awareness Campaigns: Educating healthcare professionals and the public about IDIA risk factors, early symptom recognition, and the importance of rapid reporting is vital [68]. Targeted campaigns can improve awareness among older adults and caregivers, fostering quicker diagnosis, cessation of offending drugs, and initiation of appropriate treatment.

In conclusion, preventing IDIA in older adults requires a coordinated, multi-dimensional approach encompassing personalized clinical decisions, patient empowerment, technological integration, and public health communication (Table 5). Aligning these efforts promises to significantly reduce the incidence and severity of this serious adverse drug reaction, ultimately enhancing patient safety and clinical outcomes in vulnerable elderly populations [69-70].

Table 5: Research Priorities and Future Perspectives for Idiosyncratic Drug-Induced Agranulocytosis (IDIA) in Older Adults.

Research Area	Description	Geriatric Relevance and Expected Impact
Validation of Risk Clusters	Confirming genetic, clinical, and pharmacological risk clusters across diverse populations and settings.	Ensures applicability of risk stratification tools to older adults with multimorbidity and polypharmacy.
Refinement of AI Predictive Models	Enhancing accuracy and clinical validation of AI algorithms for IDIA risk prediction.	Improves personalized risk assessment and clinical decision-making in frail elderly patients.
Evaluation of Connected Monitoring Technologies	Assessing usability, accuracy, and outcomes of telemedicine, wearable sensors, and home blood testing devices.	Addresses challenges of mobility, cognitive impairment, and healthcare access in older populations.
Development of Targeted Therapies and Biomarkers	Translational research into immune mechanisms and neutrophil biology to discover novel treatments and early markers.	Potential to reduce severity and improve prognosis, particularly for elderly patients with altered immunity.
Implementation Science and Patient Engagement	Studying effective integration of technology and education programs in clinical workflows and elderly care.	Enhances adherence, self-management, and timely intervention, crucial in cognitively or physically impaired patients.
Epidemiological Studies in Geriatrics	Large-scale studies to determine IDIA incidence, risk factors, and outcomes specifically in elderly populations.	Informs tailored preventive strategies and resource allocation for geriatric care.

Conclusion

Idiosyncratic drug-induced agranulocytosis (IDIA) remains a significant clinical challenge due to its unpredictable onset, potential severity, and the wide variety of implicated medications. This challenge is especially acute in older adults, who are more vulnerable due to comorbidities, polypharmacy, and altered physiological responses. However, the convergence of advances across multiple disciplines offers a transformative opportunity to shift from reactive to proactive, personalized care.

Progress in identifying risk clusters - through comprehensive analysis of genetic predispositions, patient demographics, comorbid conditions, and medication profiles - has laid the foundation for more targeted prevention strategies tailored to high-risk groups such as the elderly. Concurrently, the integration of big data analytics and artificial intelligence (AI) facilitates the development of sophisticated predictive models capable of estimating an individual's risk of developing IDIA prior to exposure to high-risk drugs. These models promise personalized prescribing and monitoring protocols that can reduce adverse outcomes, particularly in fragile geriatric populations.

Innovations in biological research - including pharmacogenomics, neutrophil biology, and immunopathogenesis - are deepening our understanding of IDIA mechanisms. Such insights may enable the development of targeted therapies and early detection biomarkers, which are vital for improving prognosis in older patients who often present with atypical symptoms. Mean-

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while, connected health technologies - such as wearable sensors, telemedicine platforms, and home-based blood count monitoring devices - are revolutionizing patient surveillance, allowing earlier intervention and reducing healthcare burdens, especially beneficial for elderly individuals with limited mobility or access to healthcare facilities.

By embracing this multidisciplinary toolkit, clinicians can transition toward a personalized, predictive, and preventive approach to managing IDIA, ultimately enhancing patient safety and outcomes in internal medicine and geriatrics.

However, further research is critical to fully realize these advances. This includes validating risk clusters in diverse populations, refining and clinically validating AI-driven predictive tools, and assessing the real-world effectiveness of connected monitoring technologies in elderly and multimorbid patients. Only through rigorous study and careful implementation can scientific and technological progress be translated into tangible benefits for patients at risk of this rare but serious adverse drug reaction.

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