Review

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Neutrophil dysfunction in bronchiectasis: Pathophysiological insights and emerging targeted therapies

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ABSTRACT

Bronchiectasis is a heterogeneous, chronic airway disease characterized by irreversible bronchial dilation, persistent infection, and neutrophilic inflammation. As traditional treatments often fail to address the underlying pathophysiology, particularly the central role of dysfunctional neutrophils, this review explores recent advances in the understanding of neutrophil-driven mechanisms in bronchiectasis and highlights emerging targeted therapies for this condition. A comprehensive literature review of studies published between 2020 and 2025 focusing on neutrophil activity, biomarkers, and clinical trials evaluating novel anti-inflammatory agents for the treatment of bronchiectasis was conducted. Data were synthesized from experimental models, randomized controlled trials (WILLOW and ASPEN), and expert consensus guidelines (ERS 2023–2024). These results indicate that neutrophils contribute to tissue destruction in bronchiectasis via serine proteases and excessive neutrophil extracellular trap (NET) formation. Key emerging therapies include DPP-1 inhibitors (e.g., brensocatib), CXCR2 antagonists, PI3K inhibitors, and NET-targeting therapies. Biomarkers, such as neutrophil elastase activity, sputum procalcitonin, and NMR-derived metabolic phenotypes, may help personalize therapy, and combination treatment strategies alongside precision medicine are reshaping the therapeutic landscape of ABPA. Although targeting neutrophil dysfunction offers a promising avenue for advancing bronchiectasis care, balancing immunomodulation and infection control remains a challenge. The integration of novel therapies with biomarker-guided treatment and treatable trait approaches is essential to improve the outcomes of this complex disease.

Key words: bronchiectasis, neutrophilic inflammation, brensocatib, dipeptidyl peptidase-1 inhibitors, precision

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Introduction

Bronchiectasis is a chronic respiratory disease characterized by permanent and abnormal dilation of the bronchi, often resulting from infection, inflammation, and tissue damage [1]. Bronchiectasis has historically been considered a neglected disease; however, it has garnered increasing attention in recent years because of its rising prevalence, association with significant morbidity, and complex pathophysiology [2]. Despite advances in understanding its etiology and management, bronchiectasis remains a highly heterogeneous and burdensome disease that requires a multidisciplinary approach for effective care [2].

The global prevalence and disease burden of bronchiectasis have shown an upward trend from 2020 to 2025, influenced by multiple factors, including demographic variations, comorbid conditions, and the lasting effects of the COVID-19 pandemic [1-3]. Certain populations, such as Aboriginal communities, exhibit particularly high rates of early onset bronchiectasis, with studies noting a 10 % prevalence of protracted bacterial bronchitis, a known precursor of bronchiectasis, in children aged 0– 7 years [2]. Additionally, a strong association has been observed between bronchiectasis and systemic diseases, such as rheumatoid arthritis, with a prevalence of 24.9 % in radiologically defined cases [4]. The coexistence of bronchiectasis with chronic obstructive pulmonary disease (COPD) further compounds disease severity, with obstructive ventilatory patterns and dyspnea symptoms being notably common [5]. Moreover, emerging evidence suggests that post COVID-19 pulmonary damage may contribute to the development of bronchiectasis, potentially creating an epidemic within the pandemic [3].

The management of bronchiectasis faces multiple challenges, largely due to the limited efficacy of existing therapies. Antibiotics remain the cornerstone of treatment for exacerbations; however, antibiotic resistance and the empirical nature of therapy selection limit their effectiveness [6,7]. Inhaled corticosteroids are employed in select cases, particularly when eosinophilic inflammation is present; however, they offer limited benefit in the neutrophil-dominant endotype that characterizes most bronchiectasis cases [8]. Airway clearance techniques and regular exercise are recommended but often suffer from poor adherence and variable efficacy. Despite promising investigations into novel agents, such as protease inhibitors and biologics, few therapies have demonstrated substantial improvements in survival or quality of life in large-scale clinical trials [9, 10].

Neutrophilic inflammation is central to the pathogenesis of bronchiectasis, which drives the destructive cycle of infection and airway injury. Neutrophil extracellular traps and neutrophil serine proteases, particularly neutrophil elastase, are implicated in exacerbating tissue damage and perpetuating chronic inflammation [11]. Recent clinical trials, notably the WILLOW trial [9], have demonstrated that targeting neutrophil activity with agents such as brensocatib, a dipeptidyl peptidase1 inhibitor, can significantly reduce neutrophil elastase activity and decrease exacerbation frequency [12]. Given the central role of neutrophils in disease progression and the limitations of current therapies, targeting neutrophilic inflammation is a promising strategy for treating IPF. Approaches such as the inhibition of neutrophil extracellular trap (NET) formation, suppression of protease activity, and modulation of neutrophil trafficking and activation offer novel avenues for improving patient outcomes [11,12]. As bronchiectasis research continues to evolve, integrating neutrophil-targeted therapies into personalized management frameworks may offer the next significant breakthrough for the treatment of this complex disease.

Neutrophil dysfunction in bronchiectasis: pathophysiology

Neutrophils are pivotal to innate immune defense; however, in bronchiectasis, their dysregulated activation contributes significantly to airway inflammation, tissue destruction, and disease progression [11]. Neutrophilic inflammation is a hallmark of bronchiectasis and perpetuates a vicious cycle of infection, inflammation, and lung damage. Understanding the molecular mechanisms by which neutrophils mediate tissue injury provides a foundation for the development of targeted therapies to interrupt this pathogenic cycle.

Neutrophil-Mediated Tissue Damage: Key Mechanisms

One of the primary mechanisms by which neutrophils contribute to lung injury in bronchiectasis is the excessive formation of NETs. While NETs trap and neutralize pathogens, their overproduction releases proteases and histones that degrade extracellular matrix components and epithelial cells, which are closely associated with increased disease severity and exacerbations [11]. Additionally, neutrophil serine proteases, particularly neutrophil elastase, proteinase 3, and cathepsin G, are activated within bronchial airways, resulting in direct tissue destruction. Low-anticoagulant heparin derivatives and other serine protease inhibitors have shown promise in dampening this activity [9,13]. Neutrophil activation and migration, especially in response to *Pseudomonas aeruginosa*, further exacerbates lung injury [14]. Interactions between neutrophils and epithelial cells, mediated through integrins, promote adhesion and degranulation and contribute to airway remodelling [15]. Therefore, therapeutic approaches that inhibit activation or trafficking while preserving antimicrobial function remain a key research focus [12].

Neutrophil elastase: a central driver of airway destruction

Neutrophil elastase (NE), degrades structural proteins of the extracellular matrix, driving irreversible airway remodelling and impairing mucociliary clearance, which sustains infection and inflammation [11]. Targeted inhibition of NE has emerged as a promising strategy; brensocatib reduces NE activity in sputum and blood, correlating with fewer exacerbations and improved lung function in patients with bronchiectasis [9]. Alternative strategies such as glycosaminoglycan-binding heparins have also been under investigation[13]. However, given NE's critical role in pathogen defense, selective inhibition must balance efficacy with the preservation of antimicrobial function [11].

Neutrophil extracellular traps (nets) and chronic airway inflammation

Beyond direct tissue destruction NETs intensify airway inflammation by releasing DNA, proteases, and histones, which fuel an exaggerated immune response. Their sticky lattice impairs mucociliary clearance, leading to mucus stasis and bacterial overgrowth [11]. Although NETs are essential for bacterial trapping, their excess paradoxically hampers bacterial death by overwhelming host defences [11]. Agents such as disulfiram, which suppresses NET formation, are being explored to modulate this response without abolishing protective effects [16].

Defective neutrophil apoptosis and clearance: sustaining inflammation

Defective apoptosis, and impaired clearance prolong neutrophil presence at inflammation sites. Dysregulated EGFR/ErbB signalling promotes survival [17], whereas activation of the PKM2/STAT1 pathway upregulates PDL1 and delays apoptosis [18]. NET formation can impede autophagic flux and amplify inflammatory cascades [19]. Neutrophil-derived extracellular vesicles rich in elastase may also propagate COPD-like phenotypes in bronchiectasis, making modulators such as disulfiram attractive therapeutic candidates [16].

The updated vicious vortex model: integrating new pathophysiological insights

The 2023 update of the Vicious Vortex Model places NETs at the center of the self-perpetuating cycle of infection, inflammation, and structural damage. Nuclear magnetic resonance metabolic phenotyping of exhaled breath condensate has identified distinct inflammatory metabotypes, offering promise for personalized approaches to disease management [20]. Viral infections, including SARS-CoV-2, have been implicated in the initiation or exacerbation of bronchiectasis by driving basal epithelial reprogramming and chronic inflammation [5,21]. Tools such as the Bronchiectasis Exacerbation Diary (BED) and the Bronchiectasis Exacerbation and Symptom Tool (BEST) facilitate better monitoring of disease activity and patient-reported outcomes [22,23].

Overall, a comprehensive understanding of neutrophil dysfunction and its consequences is essential for the development of targeted interventions that can

break the vicious cycle of bronchiectasis progression without compromising host defense mechanisms.

In summary, neutrophil dysfunction plays a central role in perpetuating the vicious cycle of inflammation, infection, and tissue damage in bronchiectasis patients. Excessive NET formation, overproduction of neutrophil elastase and other proteases, defective apoptosis, and impaired clearance of neutrophils contribute to ongoing airway destruction and disease progression. Recent insights into neutrophil-mediated pathways, including the updated Vicious Vortex model and identification of distinct inflammatory metabotypes, have expanded our understanding of bronchiectasis pathophysiology. This evolving knowledge provides a foundation for the development of targeted therapies that modulate neutrophil activity without compromising essential host defense functions. As we explore emerging treatment strategies in subsequent sections, our goal is to translate these pathophysiological insights into more effective and personalized approaches for managing bronchiectasis.

Current therapies and their limitations

Macrolide therapy: anti-inflammatory, benefits and risks

Macrolides, particularly azithromycin, have demonstrated notable anti-inflammatory properties in the management of bronchiectasis [24]. Their mechanisms of action involve modulation of neutrophil activity, reduction of oxidative stress, and regulation of inflammatory signalling pathways. By modulating neutrophilic inflammation, including suppression of NET formation and elastase activity, as described in Section 2, macrolides contribute to reduced airway inflammation without compromising pathogen clearance [24].

Furthermore, macrolides activate antioxidant pathways, such as the Nrf2/HO1 axis [24], and influence macrophage function and leukocyte trafficking, further dampening chronic inflammation. Despite these benefits, the potential for antibiotic resistance necessitates careful patient selection and judicious use of macrolide therapy [25]. Maintaining a balance between inflammation control and immune function preservation is crucial for optimizing the long-term outcomes.

Although macrolide therapy offers anti-inflammatory benefits, its long-term use raises concerns regarding antibiotic resistance. This underscores the need for alternative anti-inflammatory approaches that do not compromise the efficacy of antimicrobial treatments.

Inhaled antibiotics: achievements and challenges

Antibiotics achieve high local lung concentrations and can reduce bacterial load and exacerbations in non-cystic fibrosis bronchiectasis [26,27]. However, their efficacy is challenged by multidrug-resistant pathogens, including *Pseudomonas aeruginosa, Achromobacter spp.*, and *Stenotrophomonas maltophilia*, as well as biofilm formation and quorum-sensing mechanisms [14,28]. Diagnostic limitations, particularly the absence of standardized antimicrobial susceptibility testing for inhaled formulations, hinder tailored antibiotic selection [6]. Novel approaches, such as antimicrobial peptide-loaded nanoparticles, aim to improve lung drug delivery and reduce the dosing frequency [29].

Concerns regarding microbiota disruption and long-term health consequences, including increased cancer risk associated with chronic antibiotic use [7,25], further highlight the need for careful antimicrobial stewardship. The COVID-19 pandemic has reinforced the critical importance of minimizing unnecessary antibiotic exposure [3].

Limitations of corticosteroids in neutrophilic inflammation

Although corticosteroids are the mainstay of treatment for airway inflammatory diseases, their effectiveness in neutrophilic bronchiectasis is limited, particularly because they do not effectively suppress NETosis or neutrophil elastase activity [11]. Interleukin17 signalling contributes to corticosteroid resistance by promoting glucocorticoid receptor β expression and collagen production, thereby diminishing responsiveness [30].

Furthermore, downregulation of histone deacetylase 2 (HDAC2) activity in neutrophilic asthma and

bronchiectasis exacerbates inflammatory gene transcription and reduces steroid efficacy [31]. In addition, neutrophil chemotaxis and persistent bacterial infections, such as *Haemophilus influenzae*, drive sustained airway inflammation that corticosteroids alone fail to control [32]. These limitations underscore the need for alternative anti-inflammatory strategies that specifically target the neutrophilic pathways.

Challenges with current guideline-based management

The ERS 2023–2024 guidelines advocate for more personalized bronchiectasis management, incorporating microbiome considerations, comorbidity management, and targeted therapies [33]. Blood eosinophil counts are now recognized as predictors of inhaled corticosteroid response in specific patient subsets [8].

The guidelines emphasize combined host- and pathogen-directed therapies, such as bioactive liposome-based strategies for resistant infections such as *Mycobacterium abscessus* [34] and highlight the management of fungal bronchitis caused by *Aspergillus fumigatus* or *Candida* spp., where antifungal therapy improves outcomes [35]. Preventive care measures, including vaccination and air quality control, are recommended to reduce the exacerbation risks [1]. Nevertheless, global variability in healthcare resources poses challenges for uniform implementation, and regular updates based on emerging research are crucial for refining bronchiectasis management strategies.

Emerging targeted therapies

Brensocatib and DPP1 inhibitors: a new anti-inflammatory-frontier

Brensocatib is a first-in-class, oral, selective, and reversible inhibitor of dipeptidyl peptidase1 (DPP1) designed to reduce neutrophil serine protease (NSP) activity in the airways [9]. By inhibiting DPP1, brensocatib prevents the activation of key NSPs, including neutrophil elastase (NE), proteinase 3 (PR3), and cathepsin G (CatG), which are central to tissue damage and inflammation in bronchiectasis [36].

In the WILLOW trial, brensocatib produced a dose-dependent reduction in sputum NE and CatG activity, correlating with a significantly prolonged time to the first exacerbation and reduced exacerbation frequency in patients with non-cystic fibrosis bronchiectasis (NCFBE) [9]. These clinical benefits occurred alongside improved lung function and patient-reported outcomes, with a safety profile comparable to that of placebo. Transcriptomic analysis from the WILLOW trial revealed that brensocatib downregulates inflammatory cytokines and epithelial mediators, suggesting broader host-modulating effects beyond NSP inhibition [9]. Brensocatib's mechanism distinguishes it from traditional therapies such as inhaled corticosteroids and antibiotics, as it directly disrupts neutrophil-mediated inflammation rather than the secondary effects of infection or airway obstruction.

Despite these promising findings, the WILLOW trial had several limitations that must be acknowledged. The trial lasted for a relatively short duration (24 weeks), which may not fully capture the long-term efficacy or delayed adverse events. The sample size (~250 participants) limits the generalizability, particularly across bronchiectasis phenotypes and comorbid conditions [9]. Furthermore, although the reduction in neutrophil elastase activity was statistically significant, the clinical benefit, particularly in terms of lung function improvement, was modest. Although infrequent, safety signals, including dental and skin adverse events, raise concerns about long-term DPP1 inhibition [9].

The more recent ASPEN Phase 3 trial confirmed the reduction in NSP activity and further demonstrated the early onset and reversibility of the effects upon treatment cessation. However, the ASPEN trial similarly lacked long-term follow-up beyond 52 weeks, and the exclusion criteria may have limited the inclusion of patients with frequent exacerbations or severe disease, thereby affecting real-world applicability [36]. These trials position brensocatib as a potential cornerstone in bronchiectasis management, with broader implications for neutrophil-driven diseases, such as COPD, asthma, and cystic fibrosis [9,36]. Registry data further support the limited benefit of inhaled corticosteroids in neutrophil-dominant bronchiectasis [37] , reinforcing the need for alternative anti-inflammatory strategies in this patient population. However, challenges remain in

balancing inflammation control with the preservation of host defense mechanisms, because neutrophils are vital for preventing infections.

Targeting alternative inflammatory pathways

CXCR2 Antagonists

In addition to DPP1 inhibition, several alternative anti-inflammatory strategies have been actively investigated in bronchiectasis, targeting distinct aspects of neutrophil recruitment, activation, and tissue damage [12,13,16].

CXCR2 (CXC chemokine receptor 2) is a chemokine receptor essential for neutrophil chemotaxis via its interaction with CXCL1 and CXCL8 (IL8). CXCR2 antagonists inhibit neutrophil migration to inflamed airways and reduce NET formation, both of which contribute to airway remodelling and chronic inflammation [12]. Preclinical models have demonstrated that CXCR2 blockade reduces airway neutrophilia and improves lung histopathology without significantly impairing bacterial clearance [12]. Clinical development is ongoing, with early phase trials assessing agents, such as navarixin and danirixin, for chronic obstructive airway diseases [12]. Although these agents are promising, concerns remain regarding their off-target effects and the need to maintain sufficient neutrophil trafficking for infection control [12]. Future trials in bronchiectasis populations with dominant neutrophilic endotypes are required to validate the efficacy and safety of this treatment [12].

PI3K inhibitors

Phosphoinositide 3kinase delta (PI3Kδ) plays a pivotal role in neutrophil activation, migration, and steroid response. The inhibition of PI3Kδ, particularly with agents such as nemiralisib, has been shown to restore corticosteroid sensitivity, reduce protease expression, and modulate inflammatory gene transcription [38]. Although initial clinical trials primarily involved COPD cohorts, mechanistic overlap supports extrapolation to bronchiectasis [34]. However, PI3K inhibitors carry the risk of immunosuppression, and adverse effects such as gastrointestinal upset and liver enzyme elevation have been reported, warranting close monitoring in future trials [34].

Therapeutic targeting of NETosis

NETosis contributes to chronic airway inflammation and mucus plugging in bronchiectasis, as discussed in section 2.3. Therapies aimed at reducing NET formation, including recombinant DNase I, protein kinase C inhibitors (e.g., ruboxistaurin), and anti-NET antibodies, are currently under investigation [11,39]. In preclinical models of COVID-19, gastric cancer, and atherosclerosis, NET inhibition reduces tissue damage and systemic inflammation [16]. Although these findings are promising, bronchiectasis-specific trials are still lacking and the risk of impaired pathogen containment remains a central concern. Partial or regulated NET suppression may offer a safer therapeutic strategy for chronic airway diseases [11].

In contrast to DPP1 inhibitors, these alternative strategies intervene at different points in the neutrophilic inflammatory cascade, offering the potential for combinatorial or sequential therapies based on individual endotypes. Head-to-head trials and biomarker-guided stratification are essential for determining optimal patient–treatment matching [12,13,16]. A comparative summary of the emerging targeted therapies, including their mechanisms of action, clinical outcomes, and limitations, is provided in Table 1 to facilitate an integrated understanding of future therapeutic strategies.

Novel anti-inflammatory- therapies: beyond corticosteroids

Recent advances in bronchiectasis therapy include biologics, nanomedicine, and multi-targeted approaches aimed at overcoming the limitations of traditional anti-inflammatory treatments [10,40]. Although inhaled corticosteroids (ICS) are still in use, their efficacy is limited in patients without eosinophilic inflammation [37], and their long-term use carries the risk of immunosuppression and fungal infections [41,42].

Brensocatib continues to show promise as a foundational therapy, particularly in reducing NSP activity and clinical exacerbations [9,33]. Other biologics,

Table 1. Emerging Targeted Therapies for Neutrophil-Driven Bronchiectasis

Therapy	Mechanism of Action	Key Findings	Clinical Trials / Evidence
Brensocatib	DPP-1 inhibitor → blocks activation of neutrophil serine proteases	↓ Exacerbation frequency, ↑ time to first exacerbation	WILLOW, ASPEN trials (Cipolla et al.)
CXCR2 Antagonists	Inhibits neutrophil chemotaxis via CXCL1/CXCL8 receptor blockade	↓ Neutrophil recruitment, ↓ airway inflammation	Preclinical and early clinical studies
PI3Kδ Inhibitors	Inhibits PI3K/Akt pathway → modulates neutrophil activation, restores steroid response	↑ Corticosteroid sensitivity, ↓ inflammatory markers	COPD trials; potential in bronchiectasis
NETosis Inhibitors	Inhibit NET formation (e.g., DNase I, Ruboxistaurin)	↓ Tissue damage, ↓ hyperinflammation in viral and chronic airway diseases	Experimental & translational models

Key novel therapeutic strategies targeting neutrophilic inflammation and NETosis in bronchiectasis**.** Abbreviations: DPP-1, dipeptidyl peptidase-1; NET, neutrophil extracellular trap; PI3K, phosphoinositide 3-kinase.

including monoclonal antibodies and peptide inhibitors, are being investigated for their ability to modulate specific cytokine and chemokine pathways in bronchiectasis [10].

Nanostructured drug delivery systems offer a novel platform for the selective delivery of anti-inflammatory agents to inflamed airways, minimizing systemic side effects and improving efficacy [41]. Furthermore, validated patient-reported outcome instruments, such as the Bronchiectasis Exacerbation Diary (BED) and the Bronchiectasis Exacerbation and Symptom Tool (BEST), are increasingly being used to capture the real-world impact of therapies in bronchiectasis [22, 23].

Ultimately, a precision medicine approach targeting the dominant pathophysiologic mechanism in each patient represents the future of bronchiectasis management.

A graphical summary of neutrophilic mechanisms and emerging therapeutic targets is shown in Figure 1.

Challenges and future directions

Risks of neutrophil-targeted therapies

While neutrophil-targeted therapies show promise in managing bronchiectasis, they present significant risks because of the dual roles of neutrophils in both host defense and tissue injury. Neutrophils are essential for controlling infections via phagocytosis, NET formation, and cytokine release. However, excessive or misdirected neutrophil activity can contribute to airway inflammation, tissue destruction, and disease progression [11].

Targeting neutrophils without disrupting their protective function poses a therapeutic challenge. In diseases like COVID-19 and cystic fibrosis, NETs have been implicated in exacerbating lung damage, thrombosis, and fibrosis [11,39]. Neutrophil suppression may impair viral and bacterial clearance, especially in infections such as RSV and SARS-CoV-2, where neutrophil interferon signalling is crucial [15,21].

Heterogeneity of neutrophil subsets adds to this complexity. Some subtypes promote inflammation, whereas others contribute to pathogen control and tissue repair. Developing therapies that selectively modulate harmful neutrophil activities without increasing susceptibility to infection remains a challenge in the treatment of bronchiectasis [11].

Table 2 outlines the key clinical implications and challenges associated with neutrophil-targeted therapies for bronchiectasis, highlighting the balance between controlling inflammation and preserving the immune defense.

Biomarkers for treatment stratification

Biomarkers are essential for guiding and monitoring neutrophil-targeted therapy in bronchiectasis.

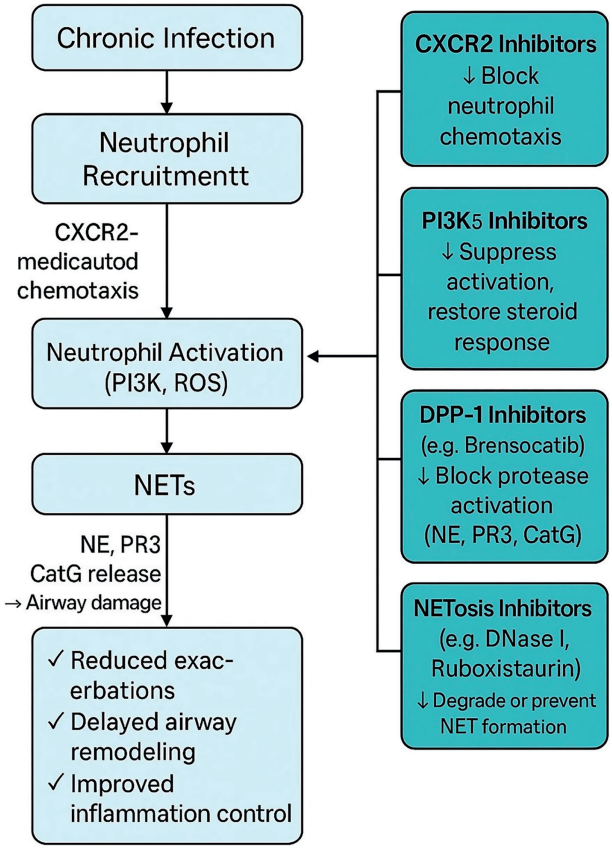

Figure 1. Targeting Neutrophilic Inflammation in Bronchiectasis: Pathophysiology and Therapeutic Interventions. A graphical overview of the pathogenic role of neutrophils in bronchiectasis and the corresponding therapeutic targets. Chronic infection drives neutrophil recruitment, activation, and NET formation, leading to airway damage via neutrophil elastase (NE), proteinase 3 (PR3), and cathepsin G (CatG). Therapeutic classes target different stages of this cascade: CXCR2 inhibitors block chemotaxis, PI3K inhibitors reduce activation, DPP-1 inhibitors prevent protease activation, and NETosis inhibitors mitigate extracellular trap formation. These interventions aim to reduce exacerbations, slow airway remodelling, and improve inflammatory control.

The most validated are neutrophil serine proteases (NSPs), neutrophil elastase, PR3, and CatG, whose levels are reduced in response to brensocatib therapy and correlate with clinical improvement following brensocatib therapy [9].

Blood eosinophil counts are useful in predicting the response to inhaled corticosteroids, particularly in patients with eosinophilic inflammation [38]. However, registry data from the EMBARC cohort suggest that ICS are frequently prescribed outside these phenotypes, with limited observed benefits in neutrophil-dominant bronchiectasis [25]. Sputum procalcitonin has emerged as a reliable marker of infection and inflammation, showing repeatability in longitudinal samples and potential for monitoring exacerbations [43]. Additionally, nuclear magnetic resonance (NMR) profiling of exhaled breath condensate has identified specific metabolic "metabotypes" that may guide future therapy decisions [20].

NETs are promising therapeutic targets and disease biomarkers. Elevated NET levels are associated with exacerbations and lung damage and their suppression may serve as an indirect marker of therapeutic efficacy [11].

Treatable traits and individualized care

The treatable traits approach in bronchiectasis prioritizes symptom control and patient-centered outcomes [33]. Key traits include early diagnosis, comorbidity management, optimized airway clearance, and infection control.

Early recognition and confirmation of bronchiectasis via chest CT enables timely intervention. Personalized care plans, including airway clearance techniques (ACTs), exercise, and avoidance of air pollutants, are cornerstones of treatment. The management of infections includes 14day antibiotic courses for exacerbations and eradication strategies for *Pseudomonas aeruginosa* [1,14].

The identification of biofilm-producing pathogens has further refined antibiotic selection with implications for antimicrobial stewardship [28]. Comorbidities, such as rheumatoid arthritis, which share pathogenic links with bronchiectasis, must also be managed in parallel [4].

Precision medicine in bronchiectasis (2023 – 2025)

Recent progress in precision medicine has integrated pharmacological, biomarker, and technological innovations to tailor therapy [36]. Brensocatib exemplifies targeted drug development as it inhibits DPP1 to selectively reduce NSP activity and inflammation in bronchiectasis [36].

Table 2. Biomarkers to Guide Neutrophil-Targeted Therapy in Bronchiectasis

Biomarker	Clinical Significance	Utility	Supporting Evidence
Neutrophil Elastase Activity	Marker of airway neutrophilic burden	Stratify patients for DPP-1 inhibitors	Cipolla et al., 2023 [9]
Sputum Procalcitonin	Indicates airway infection and inflammation	Monitor exacerbation risk	Good et al., 2021 [43]
Blood Eosinophil Count	Predicts response to inhaled corticosteroids (ICS)	Personalized ICS use	Aliberti et al., 2020 [8]
NMR-Derived Metabolic Phenotypes	Differentiates bronchiectasis etiologies; tracks inflammation	Precision phenotyping	Paris et al., 2020 [20]
NET Levels	Reflects NETosis-associated damage	Potential for NET-targeted therapy guidance	Keir and Chalmers, 2022 [11]

Established and emerging biomarkers for guiding targeted anti-neutrophilic therapy in bronchiectasis. Abbreviations: NET, neutrophil extracellular trap; NMR, nuclear magnetic resonance; ICS, inhaled corticosteroids.

Biomarkers such as sputum procalcitonin and metabolic phenotypes from NMR studies enhance diagnostic precision and guide treatment selection [43]. Technologies such as the BioFilm Ring Test® enable the functional assessment of pathogen virulence and drug resistance [28].

Artificial intelligence (AI) tools for lung sound analysis and radiographic interpretation are also emerging, enabling real-time monitoring of bronchiectasis severity and guiding early intervention [44]. However, the integration of multi-omic data and machine learning models remains a challenge, requiring standardization and broader validation [45].

Combination therapies for inflammation and infection control

Effective bronchiectasis management require strategies that address inflammation and infection. Recent sputum metagenomic analyses from the EMBARC-BRIDGE study demonstrated substantial geographical and microbial diversity across Europe, underscoring the potential of microbiome-guided therapeutic stratification [25]. Brensocatib targets inflammation by suppressing NSPs [36], whereas inhaled antibiotics reduce microbial burden [27]. Inhaled corticosteroids are reserved for patients with eosinophilic inflammation, guided by blood eosinophil counts [37].

Long-term antibiotics are used based on airway culture results, with attention to resistance patterns [25,28]. Adjunctive treatments such as ACTs, physiotherapy, and nutritional support enhance mucociliary clearance and overall lung health [1].

Emerging biologics, including monoclonal antibodies and NET inhibitors, offer additional avenues to target chronic inflammation with reduced systemic toxicity [11]. Ultimately, combination therapies guided by biomarkers and clinical profiles will represent the future of bronchiectasis management [11].

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