Review

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From Sinuses to Bronchi: Molecular Endotypes and Therapeutic Convergence in CRS-Asthma Comorbidity

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Chronic rhinosinusitis (CRS) and asthma represent interrelated inflammatory disorders within the unified airway continuum, sharing overlapping molecular and immunologic mechanisms, clinical features, and therapeutic responses. Epidemiological studies indicate a high prevalence of CRS-asthma comorbidity, which is associated with increased disease severity, healthcare utilization, and impaired quality of life compared with either condition alone. Advances in airway immunology have established type 2 (T2) inflammation, characterized by epithelial barrier dysfunction, eosinophilic infiltration, and cytokine signaling via interleukin (IL)-4, IL-5, IL-13, thymic stromal lymphopoietin (TSLP), and IL-33, as a central pathogenic axis across both upper and lower airways. Non-type 2 (non-T2) endotypes contribute to disease heterogeneity and treatment resistance. This review synthesizes current evidence on shared molecular endotypes, emerging biomarkers, and clinical consequences of CRS-asthma comorbidity, with particular emphasis on biologic therapies targeting immunoglobulin E (IgE), IL-5, and multi-omics profiling and artificial intelligence-assisted analytics, in refining disease stratification, predicting therapeutic response, and guiding integrated treatment strategies. Finally, we highlight key research gaps and propose future directions toward endotype-driven, unified airway care aimed at improved long-term outcomes for patients with CRS-asthma comorbidity.

Keywords: CRS; asthma; unified airway; type 2 inflammation; ESS; precision medicine; immunomodulation

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Introduction

The respiratory tract has traditionally been divided into the upper and lower airways at the level of the vocal cords. However, this distinction is largely anatomical rather than biological. Both compartments are anatomically continuous and share epithelial, neural, and immunological networks that support the concept of the unified airway. The unified airway disease (UAD) hypothesis proposes that the upper and lower respiratory tracts function as a single integrated organ system, with diseases such as asthma, allergic rhinitis, and chronic rhinosinusitis (CRS) representing distinct manifestations of a shared inflammatory process [1–3]. Mechanistic links between the sinonasal and bronchial mucosa include aspiration of inflammatory mediators, hematogenous dissemination of cytokines, activation of bone marrow progenitors, and the naso-bronchial reflex. Historically exemplified by the asthma-allergic rhinitis axis, this paradigm has evolved to encompass broader airway phenotypes, including CRS with nasal polyps (CRSwNP), bronchiectasis, and chronic obstructive pulmonary disease (COPD), highlighting a complex and heterogeneous disease continuum across airway compartments [4–6].

CRS represents a spectrum of disorders characterized by persistent inflammation of the sinonasal mucosa for ≥12 weeks, presenting with at least two of the following: nasal obstruction, nasal discharge, facial pain or pressure, and olfactory dysfunction, supported by endoscopic or radiologic evidence [7,8]. CRS has two distinct subtypes, which include CRSwNP, which is determined by endoscopic examination results. The worldwide population is affected by CRS, which reduces their productivity and increases their medical costs, thus creating a major social and economic impact that affects 5 to 28 percent of people worldwide. The link between CRS and asthma has been confirmed through studies, which show that both conditions share common type 2 (T2) inflammatory patterns, and their respective epithelial barriers become damaged while they produce local immunoglobulin E (IgE) in both conditions [9,10]. Asthma develops in more than 40% of patients with CRSwNP, while additional medical conditions lead to increased eosinophil counts, elevated local IgE levels, and more severe disease symptoms. The results demonstrate that upper airway inflammation and lower airway inflammation share an immunological pathway that connects both types of respiratory tract inflammation.

The combination of CRS and asthma demonstrates the clinical importance of UAD because one airway zone displays inflammation, which affects the control of the disease and its expected outcome in the other zone. Patients with CRSwNP and comorbid asthma typically exhibit more severe symptoms, increased corticosteroid dependence, higher recurrence rates after surgery, and diminished quality of life [3]. The nasal and bronchial biopsy inflammatory profiles establish histological evidence that shows that airway interdependence exists between those two structures. The T2 inflammatory response of the body shows two major types of non-eosinophilic endotypes, which include neutrophilic chronic rhinosinusitis and non-allergic eosinophilic asthma, and non-allergic rhinitis with eosinophilia syndrome (NERES). Recognition of such shared but diverse endotypes is revolutionizing clinical management from an organ-based management toward an endotype-based precision management [11–13]. This shift has revealed that existing guideline-based methods, which use symptoms and risk factors to classify disease severity, do not adequately measure the complex relationships between airway inflammation and mucosal defense breakdown, and external factors, which include infection and pollution [14,15].

This review aims to synthesize current evidence on the molecular, immunological, and clinical convergence between CRS and asthma within the unified airway framework. We critically examine epidemiological trends, shared endotypes, and mechanistic pathways, including epithelial barrier dysfunction, cytokine networks (interleukin (IL)-4, IL-5, IL-13, thymic stromal lymphopoietin (TSLP), IL-33), local IgE synthesis, and microbiome dysbiosis and their implications for disease severity and treatment outcomes. By highlighting biomarkers, precision medicine strategies, and biologic therapies such as anti-IgE, anti-IL-5, and anti-IL-4R agents, we discuss how therapeutic advances targeting one airway compartment can yield benefits across both compartments. Finally, we identify existing research gaps, propose directions for biomarker-guided treatment algorithms, and advocate for a unified, endotypes-based clinical framework that integrates upper and lower airway care within the precision medicine era.

Epidemiology and Clinical Burden

The global estimation of CRS prevalence shows unreliable results because different studies use distinct diagnostic methods and research frameworks. The EPOS 2020 position papers, together with extensive population studies, show that adult populations experience CRS prevalence rates between 8 percent and 12 percent [7,16]. Epidemiological modeling shows a strong bidirectional relationship between CRS and asthma according to its clinical implications. Around 25 to 30 percent of CRS patients also develop asthma, while 22 to 45 percent of asthmatic people show CRS symptoms, with the highest incidence between CRS with nasal polyps and type 2-high inflammatory endotypes [17,18]. Patients with CRS-asthma comorbidity experience greater disease burden, increased symptom severity, and reduced quality of life compared with patients affected by either condition alone. Validated assessment tools, including the Sino-Nasal Outcomes Test-22 (SNOT-22) and Asthma Control Test (ACT), demonstrate that patients with overlapping upper and lower airway disease experience more severe respiratory symptoms and impaired daily functioning. These findings support the need for integrated diagnostic and therapeutic approaches targeting shared inflammatory mechanisms rather than treating CRS and asthma as isolated disorders [19–21]. The CRS-asthma comorbidity creates a severe quality of life reduction for people because it affects more than their economic well-being. The Sino-Nasal Outcomes Test-22 (SNOT-22) and asthma control test (ACT), which are validated assessment tools, show that patients with multiple conditions experience greater symptom burden across their entire respiratory system. The observed results demonstrate that integrated diagnostic and therapeutic methods need to address shared inflammatory drivers that affect both CRS and asthma instead of treating these conditions as separate medical disorders [22,23].

Clinical Phenotypes and Immuno-Endotypes

The clinical and molecular heterogeneity of CRS and asthma shows how genetic factors, environmental factors, and immunologic factors interact with one another to create complex medical conditions. The identification of clinical presentation phenotypes needs to be separated from the identification of endotypes, which stem from fundamental biological pathways to enable researchers to predict disease progression and treatment outcomes [24,25]. This section delineates key clinical subtypes of CRS and asthma, explores the immunologic networks that define type 2 (T2) and non-type 2 (non-T2) inflammation, and highlights cross-endotype features such as tissue eosinophilia and IgE-mediated responses and epithelial remodeling, which unify airway disease biology.

CRS Phenotypes: CRSwNP vs. CRSsNP

Chronic rhinosinusitis is traditionally classified into two major clinical phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRSwNP presents itself through eosinophilic type 2-driven inflammation, which leads to increased production of IL-4, IL-5, and IL-13. In contrast, CRSsNP displays a neutrophilic pattern, which shows Th1 and Th17 cytokines as its main cytokine components [26,27]. CRSwNP patients experience greater nasal obstruction and decreased ability to smell, and they have higher surgical recurrence rates. Recent research using single-cell analysis and transcriptomic studies has identified molecular subclusters in CR-

SwNP, which display unique patterns of inflammation and impaired epithelial barrier function and Staphylococcus aureus colonization-related localized IgE production [28,29]. CRSsNP exhibits both epithelial barrier dysfunction and fibrosis development, but shows reduced eosinophilic infiltration compared to other conditions. The different physical characteristics of the two conditions lead to different treatment outcomes because current biologic treatments for T2 inflammation require precise diagnosis under their clinical practice guidelines [30].

Asthma Phenotypes in the Context of CRS

The airway disease spectrum of asthma, which is linked to chronic rhinosinusitis, presents a clinical picture that corresponds with the unified airway hypothesis. People with asthma demonstrate different phenotypes, which include three allergic subtypes, three nonallergic subtypes, two eosinophilic subtypes, one neutrophilic subtype, and one paucigranulocytic subtype. The highest occurrence of CRS comorbidity occurs in patients who develop eosinophilic asthma after reaching adulthood, especially in those who suffer from CRSwNP or aspirin-exacerbated respiratory disease (AERD) [31]. The individuals experience worse asthma management because they need additional corticosteroids, and their lung capacity decreases when compared to asthmatics who do not have CRS. The study found that patients' bronchial inflammation corresponds with their sinonasal inflammation, as both conditions share a common systemic endotype rather than having separate disease compartments. The study results show that patients exhibit an inflammatory pattern that requires healthcare providers to use comprehensive management methods [32–34].

Type 2 and Non-T2 Inflammatory Endotypes

The study investigates T2 and non-T2 forms of inflammation. T2 inflammation, which occurs through IL-4, IL-5, and IL-13 pathways, activates T helper 2 (Th2) cells and group 2 innate lymphoid cells (ILC2s) and leads to eosinophil accumulation in affected tissues. The condition exists in most patients who have CRSwNP, allergic asthma, and AERD [11,35]. The non-T2 endotypes exhibit Th1 and Th17 immune responses because their neutrophilic and mixed granulocyte patterns depend on interferon gamma (IFN-γ), IL-17A, and tumor necrosis factor alpha (TNF-α). Infection, pollution exposure, and corticosteroid resistance commonly lead to non-T2 inflammation. Advanced techniques such as cytometry by time-of-flight (CyTOF) and single-cell RNA sequencing (scRNA-seq) have revealed subpopulations within these endotypes, which enable researchers to develop more accurate treatment approaches for specific therapies. The identification of these immunologic pathways enables clinicians to use biologics for endotype-specific treatments that block T2 cytokine signaling and IgE-mediated signaling pathways [36–38].

Aspirin-Exacerbated Respiratory Disease (AERD) as a Unified Endotype

AERD shows that airway inflammation affects the entire body because it connects CRS with asthma and shows hypersensitivity to cyclooxygenase-1 (COX-1) blockers. The disease manifests through strong T2-high eosinophilic inflammation, which shows impaired arachidonic acid metabolism because of decreased prostaglandin E2 (PGE2) production and excessive leukotriene synthesis [39]. The analysis of transcriptomic and lipidomic data shows that both upper and lower airways share inflammatory mediators, which include IL-5 and CCL26 (eotaxin-3) and cysteinyl leukotrienes. AERD patients show severe polyposis, which occurs repeatedly, and they respond poorly to corticosteroids, so they need multiple surgical procedures. The research shows that biologics, which target IL-5 and IL-4Rα (mepolizumab and dupilumab), provide better asthma and sinus control to AERD patients who demonstrate the condition as a single systemic endotype instead of two distinct diseases [40–42].

Cross-Endotype Features: Tissue Eosinophilia, IgE, and Mucosal Remodelling

The immunopathologic features exhibit molecular connections between CRS and asthma that exist beyond the boundaries of standard phenotypic classification. Tissue eosinophilia functions as a T2 inflammation marker, which links to disease severity, polyp recurrence, and diminished corticosteroid treatment outcomes [43,44]. The production of local IgE by nasal and bronchial mucosae leads to increased mast cell activation, which results in sustained chronic inflammation that affects both atopic and nonatopic individuals. Epithelial remodelling, including basal cell hyperplasia, goblet cell metaplasia, and subepithelial fibrosis, contributes to irreversible airflow obstruction and sinus ostial narrowing. Recent proteomic and transcriptomic studies reveal that these remodelling processes are driven by persistent IL-13 signalling and epithelial-mesenchymal transition (EMT) [45]. Collectively, these cross-endotype mechanisms illustrate a shared inflammatory and structural remodelling axis that supports the concept of a unified airway disease continuum.

Pathophysiological Mechanisms at the Unified Airway

The concept of the UAD is supported by converging anatomical, immunological, and molecular evidence linking the upper and lower respiratory tracts as a continuous inflammatory unit. The nasal and bronchial mucosa share common structural components, including ciliated pseudostratified epithelium, basement membrane, lamina propria, and submucosal glands, forming a single immunologic interface exposed to environmental allergens, pathogens, and pollutants [1,46–48]. Inflammation at one site can propa-

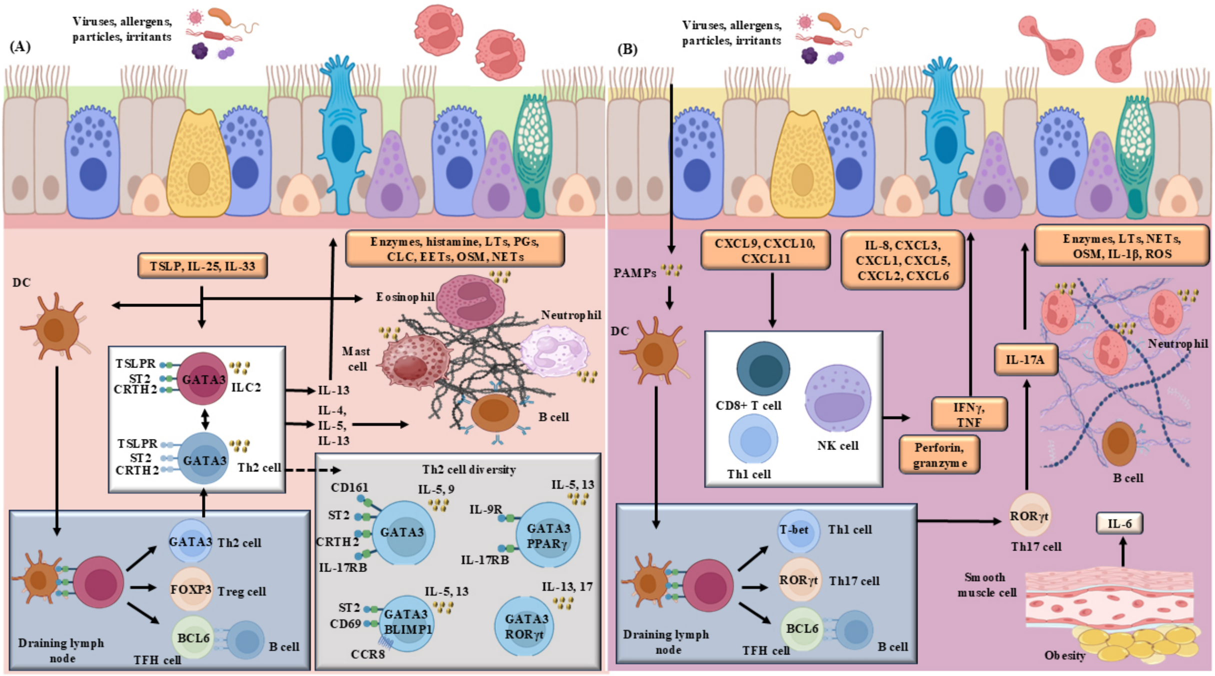

Fig. 1. Immunological mechanisms underlying type 2 and non-type 2 inflammation in asthma and chronic rhinosinusitis. The figure (A) shows how chronic inflammation affects both upper and lower airway systems through their linked cellular and molecular pathways. Epithelial barrier breakdown in the sinonasal and bronchial mucosae starts the release of alarmins, which include thymic stromal lymphopoietin, interleukin 33, and interleukin 25 that activate dendritic cells and group 2 innate lymphoid cells. The upstream signals lead to T helper 2 cell differentiation and activation through GATA3 transcription factor control, which results in type 2 cytokine production of interleukin 4, interleukin 5, and interleukin 13. The combination of IL-4 and IL-13 drives immunoglobulin E (IgE) class switching together with excessive mucus production and changes in epithelial structure, whereas IL-5 drives the development, recruitment, and survival of eosinophils. (B) shows eosinophils, mast cells, and basophils activate inflammatory pathways through their release of cytokines and production of leukotrienes and their ability to cause tissue damage, which leads to the development of nasal polyps, increased airway sensitivity, and asthma attacks. The transcription factor FOXP3 establishes Regulatory T cells (Tregs) as immune system components that suppress excessive immune system activity; Treg function impairment, which occurs in CRS-asthma comorbidity, leads to ongoing inflammation. B-cell lymphoma 3 (BCL3) functions as an additional transcriptional regulator that affects the expression of inflammatory genes and takes part in determining how chronic diseases progress and how patients respond to corticosteroids. The figure demonstrates that non-type 2 inflammatory pathways operate through Th1- and Th17-mediated responses, which lead to neutrophilic inflammation and decrease the effectiveness of corticosteroids and current biologic therapies. The three mechanisms demonstrate that shared immune system elements between the unified airway system lead to different disease patterns, treatment failures, and increased clinical problems for patients who have CRS-asthma comorbidity, which supports the need for endotype-specific and targeted treatment methods. Abbreviations: CLC, Charcot-Leyden crystals; EETs, eosinophil extracellular traps; LTs, leukotrienes; NETs, neutrophil extracellular traps; OSM, oncostatin M; PGs, prostaglandins; PPARγ, peroxisome proliferator-activated receptor-γ; DC, dendritic cell; PAMPs, pathogen-associated molecular patterns; GATA3: GATA binding protein 3; FOXP3, Forkhead box P3. The figure was created using Microsoft PowerPoint 2021 (Microsoft Corporation, Redmond, WA, USA) and Adobe Illustrator 2023 (Adobe Inc., San Jose, CA, USA).

gate systemically or locally to the other through hematogenous mediators, neural reflexes, and epithelial-immune crosstalk. This section delineates the key mechanistic pillars underpinning CRS-asthma comorbidity within the unified airway framework, emphasizing epithelial barrier dysfunction, cytokine orchestration, alarmin signaling, IgE-mediated immunity, microbiome dysbiosis, and neuroimmune remodelling [2,49,50]. Table 1 (Ref. [36,51–56]) further elaborates the cytokines and immune pathways.

Shared Immunopathology of CRS and Asthma

CRS and asthma share convergent immunological mechanisms rooted in epithelial barrier dysfunction and dysregulated innate and adaptive immune responses [57,58]. In type-2-high disease, epithelial injury promotes the release of alarmins such as TSLP, IL-33, and IL-25, which activate ILC2s and Th2 cells [59–61]. This cascade drives IL-4, IL-5, and IL-13 production, resulting in eosinophilic

Table 1. Key cytokines and immune pathways implicated in chronic rhinosinusitis (CRS) and asthma comorbidity.

Cytokine/pathway	Source cells	Principal pathogenic role	Representative agents; therapeutic target; stage of application	Ref.
IL-4	Th2 cells, ILC2s, mast cells, basophils	Drives IgE class switching; promotes B-cell differentiation and mucus production; amplifies eosinophilic inflammation	Dupilumab (anti-IL-4Rα; blocks IL-4/IL-13 signaling; approved); Pitrakinra (IL-4R antagonist, experimental)	[51]
IL-5	Th2 cells, ILC2s, eosinophils	Promotes eosinophil differentiation, recruitment, and survival; key effector of type 2 inflammation	Mepolizumab, Reslizumab (anti-IL-5; approved); Benralizumab (anti-IL-5Rα; approved)	[52]
IL-13	Th2 cells, ILC2s, epithelial cells	Induce goblet cell hyperplasia, mucus hypersecretion, airway remodeling, and fibrosis	Dupilumab (shared IL-1Rα blockade; approved), Lebrikizumab, Tralokinumab (anti-IL-13, investigational)	[51]
TSLP	Airway epithelial cells, fibroblasts, and mast cells	Initiates type 2 inflammation by activating dendritic cells and ILC2s; enhances Th2 polarization	Tezepelumab (anti-TSLP; approved for asthma, emerging role in CRS)	[53]
IL-33/ST2 Axis	Epithelial cells, endothelial cells, fibroblasts	Potent alarmin driving eosinophilic and ILC2 responses; promotes airway hyperresponsiveness	Etokimab (anti-IL-33; trials), Itepekimab, Astegolimab (anti-ST2, clinical trials)	[53]
IL-25 (IL-17E)	Epithelial cells, Tuft cells	Amplifies type 2 responses via ILC2 and Th2 activation; synergistic with TSLP/IL-33	IL-25 receptor-targeting antibodies (preclinical/early development)	[53]
IgE/FcɛR1 Pathway	B cells, plasma cells, mast cells, basophils	Mediates allergic sensitization and mast cell degranulation; cross-links with epithelial barrier dysfunction	Omalizumab (anti-IgE; approved)	[54]
Eotaxins (CCL11, CCL24, CCL26)	Epithelial cells, fibroblasts, eosinophils	Recruit eosinophils via CCR3; amplify tissue infiltration and remodeling	CCR3 antagonists (preclinical/early clinical development)	[36]
Leukotrienes (LTB4, LTC4, LTD4)	Mast cells, eosinophils	Promote bronchoconstriction, vascular permeability, and eosinophil chemotaxis	Montelukast, Zafirlikast, Pranlikast (leukotriene receptor antagonists; approved)	[55]
TGF-β/Remodeling Axis	Epithelial cells, fibroblasts, and macrophages	Induces subepithelial fibrosis, smooth muscle hypertrophy, and tissue remodeling	Losartan (TGF-β modulation; repurposed), anti-TGF-β monoclonal antibodies (clinical trials)	[56]

IL, interleukin; Th2, T helper 2; ILC2s, group 2 innate lymphoid cells; IgE, immunoglobulin E; TSLP, thymic stromal lymphopoietin; CCL11, C-C motif chemokine ligand 11; LTB4, leukotriene B4; LTC4, leukotriene C4; LTD4, leukotriene D4; TGF-β, transforming growth factor beta; CCR3, C-C motif chemokine receptor 3.

inflammation, IgE synthesis, mucus hypersecretion, and tissue remodeling across both upper and lower airways. These mechanisms are well established and form the biological basis for shared therapeutic targets.

Emerging Role of the Airway Microbiome

Recent primary studies (2022–2025) have identified airway microbiome dysbiosis as the main factor that changes the CRS-asthma endotype. The research demonstrates that decreased microbial diversity, together with increased *Staphylococcus aureus* and *Haemophilus* influenzae pathogens, causes greater type 2 inflammation and damages epithelial barriers, and leads to worse results with corticosteroid treatment [62–64]. Longitudinal sequencing studies demonstrate that changes in microbial populations occur before clinical exacerbations, which establishes the microbiome as a dual function that serves as both a biomarker and a possible treatment target [65].

Neuroimmune Interactions in the Unified Airway Disease

Neuroimmune crosstalk has emerged as an essential but insufficiently studied mechanism that causes airway inflammation. Sensory neurons release neuropeptides, which include substance P and calcitonin gene-related peptide (CGRP), to boost local immune responses through their effects on vascular permeability and mast-cell activation, and cytokine production [66–68]. Recent experimental and clinical studies demonstrate that neuroimmune signaling affects symptom severity, pain perception, and airway hyperresponsiveness in both CRS and asthma. This discovery reveals a new biological pathway that has potential medical applications [69–72]. The research results demonstrate that two different immunopathological pathways lead to the same clinical symptoms of CRS and asthma. The Type 2 inflammation pathway begins when epithelial cells release alarmins (TSLP, IL-25, IL-33), which activate Th2 and ILC2 pathways to produce eosinophils and cause IgE-based diseases. In contrast, non-type 2 disease involves Th1- and Th17-skewed immunity with neutrophilic infiltration and epithelial injury [73]. These interconnected pathways are illustrated in Fig. 1, which integrates the cellular and molecular mechanisms underpinning type 2 and non-type 2 inflammation across the unified airway continuum.

Impact of CRS on Asthma Control and Severity

A growing body of clinical and molecular evidence supports the bidirectional inflammatory continuum between CRS and asthma, central to the unified airway hypothesis. Epidemiologically, up to 38% of patients with allergic rhinitis exhibit coexisting asthma, and conversely, nearly half of asthmatics present with upper airway disease [74,75]. Radiologic studies demonstrate that as many as 80% of asthmatic patients show sinus abnormalities, even in the absence of overt nasal symptoms. This strong coprevalence highlights shared pathogenic mechanisms linking upper and lower airway inflammation [76,77]. Mechanistic studies suggest that CRS exacerbates bronchial inflammation through multiple pathways, including aspiration of inflamed sinus secretions, enhanced vagal reflexes, mouth breathing-induced airway desiccation, and, most importantly, systemic propagation of T2 inflammatory mediators. The respiratory tract experiences eosinophilic inflammation because the cytokines IL-4, IL-5, IL-13, IL-33, and epithelial alarmins TSLP and IL-25 activate this process. Eosinophils and type 2 innate lymphoid cells (ILC2s) work together to create a connection that increases Th2 cytokine production while maintaining long-term inflammation. The research demonstrates that CRS and asthma exist as one unified disease, which causes inflammation throughout the respiratory system instead of two separate conditions that affect specific areas [78].

Clinical observations establish that asthma control and exacerbation risk both suffer from the presence and intensity of CRS symptoms. The surgical cohorts of patients with recalcitrant CRS showed that their radiologic severity according to Lund-Mackay score (LMS) assessments directly correlated with their asthma severity according to National Institutes of Health (NIH) criteria [79,80]. Patients with severe asthma demonstrate increased LMS and higher rates of nasal polyposis and atopy, which show their systemic eosinophilic phenotype. The connections between these two variables remain intact because radiologic evaluations show weak links to patient-reported symptom assessments, which prove the diagnostic worth of imaging-based CRS evaluations. Research studies show that managing upper airway disease results in better asthma control. The results of functional endoscopic sinus surgery (FESS) show that the procedure decreases asthma symptoms and inhaler usage and systemic corticosteroid needs, which leads to 90% of patients reporting personal progress, while more than two-thirds experience fewer asthma attacks. The study results demonstrate that airway maintenance depends on two things, which include maintaining sinonasal health and controlling bronchial inflammation. The study results demonstrate that airway maintenance depends on two things, which include maintaining sinonasal health and controlling bronchial inflammation [81,82].

Patients who have both CRS and asthma experience more rapid lung function deterioration because their condition includes nasal polyposis. Severe asthmatics who have CRS show more extensive endoscopic and CT examination results while experiencing lower forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) measurements than nonsevere asthmatics [83,84]. The molecular analysis of nasal tissue samples from these patients shows that Th2 cytokines (IL-4, IL-5, IL-9, IL-13) and alarmins (IL-33, IL-25, TSLP) are present in increased levels, which leads to worsened asthma symptoms and restricted breathing ability. The researchers found that ILC2s, which show dual expression of Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) and Suppression of Tumorigenicity 2 (ST2), act as the main cause of inflammation that does not respond to steroids. The patients continue to produce these cytokines together with nasal tissues, which remain active despite treatment with topical corticosteroids, indicating that they have developed resistance to both local and systemic corticosteroid effects [85]. Experimental evidence indicates that TSLP signaling may protect ILC2s from glucocorticoid-induced apoptosis, which results in ongoing inflammation during conventional treatment. The molecular relationship between CRS and severe asthma demonstrates that targeting the LL-33/ILC2 axis and IL-1Rα pathways with biologic agents such as dupilumab and tezepelumab will restore steroid responsiveness while improving results throughout the entire airway system [86,87].

The combination of CRS and asthma causes more than just physical health problems, which leads to a significant decrease in health-related quality of life (HRQoL) for patients. Patients with dual disease report higher symptom scores, increased fatigue, sleep disturbance, and reduced work productivity compared with those with either condition alone [88,89]. The medical imaging and endoscopy techniques fail to match the patient assessment results from the SNOT-22 test because they do not align with each other. Asthmatic patients who have CRS experience a higher overall symptom burden than their counterparts who do not have this condition. Both medical and surgical treatment methods, together with biologic treatments of CRS, lead to measurable enhancements of quality of life, which affects both upper and lower airway medical conditions, because the treatments address all aspects of airway inflammation. The growing success of biologic therapies throughout respiratory conditions requires HRQoL measurements to become primary endpoints in upcoming studies because they assess patient-centered health outcomes [90,91].

Biomarkers and Precision Medicine Approaches

Recent advances in airway immunology have accelerated the transition from phenotype-based to endotype-driven management of CRS and asthma. The medical field uses biomarkers, which demonstrate epithelial dysfunction together with type 2 cytokine signaling and systemic inflammation, to classify patients and determine their response to biologic treatment while assessing their treatment results [92,93]. The combination of molecular signatures from nasal secretions, blood, and exhaled breath condensates establishes a precision medicine system that uses patient-specific inflammatory patterns for selecting and scheduling their treatment (Table 2, Ref. [54,92–100]). The biomarker-guided system establishes disease classification while it connects the shared biological mechanisms that exist between the upper and lower airway systems within topographical airway systems.

Systemic and Local Biomarkers

Biomarkers function as measurable indicators that track both disease processes and treatment outcomes, establishing themselves as the fundamental components of precision medicine used in multiple airway disorders [96,100]. Systemic biomarkers that track T2 activity include blood eosinophil counts, fractional exhaled nitric oxide (FeNO) levels, and IgE measurements of total and allergen-specific IgE. These biomarker tests have been validated to predict both disease severity and treatment response to biologic therapies that target T2 pathways [101,102].

Scientists utilize nasal swabs, lavage samples, and tissue biopsies to detect local biomarkers that help them study airway inflammation. The combination of increased nasal IL-5 and periostin and eotaxin-3 levels indicates the presence of eosinophilic infiltration, while nasal nitric oxide (nNO) levels show an inverse relationship with both mucosal obstruction and disease activity. The detection of TSLP, IL-33, and IL-25 in sinonasal tissue demonstrates their function as epithelial alarm signals that activate both local and systemic inflammatory responses. The combination of systemic blood and FeNO measurements with local nasal or sputum biomarkers enables doctors to assess airway inflammation through multiple methods, which help them detect dual-compartment T2-high disease more effectively [53,103].

Tissue-based Predictors of Dual Disease Activity

The identification of inflammatory endotypes that affect both upper airway and lower airway tissues depends on tissue-based biomarkers. The higher levels of IL-5 and IL-13 and eosinophil cationic protein (ECP) in patients with CRS who also have nasal polyps (CRSwNP) connect their sinonasal tissue damage to increased bronchial eosinophilia and worsened asthma control, which leads to hyperresponsive lower airway conditions [104,105]. The IL-33/ILC2 axis has become a central immunological pathway that links various immune functions in the body. The study found that severe asthmatics have increased type 2 innate lymphoid cells, which show CRTH2 and ST2 receptor expression in their chronic rhinosinusitis tissues. The activation of these cells leads to Th2 cytokine transcription, which includes IL-5, IL-9, and IL-13. This process results in decreased lung capacity [106,107].

The research results show that sinonasal tissue cytokine profiles can measure asthma severity through their potential to function as predictive biomarkers. The ongoing presence of these inflammatory substances, which continue to exist despite corticosteroid treatment, demonstrates the existence of steroid-resistant endotypes that require treatment with biological drugs that block Il-4Rα and IL-5 pathways. The discovery of tissue-based predictors enables the development of a diagnostic system that uses upper airway biopsy results to determine treatment approaches that address lower airway conditions.

Table 2. Predictive biomarkers for CRS-asthma disease activity and treatment response.

Biomarker	Specimen type	Associated endotype/pathway	Predictive value/clinical relevance	Reference utility
Blood eosinophil count	Peripheral blood	Type 2 (IL-5-driven eosinophilic)	Correlates with CRS and asthma severity; predicts response to anti-IL-5 and corticosteroids; surrogate for eosinophilic inflammation	Widely validated in clinical trials and real-world studies [94]
Fractional exhaled nitric oxide (FeNO)	Exhaled air	Type 2 (IL-13-mediated epithelial activation)	Reflects airway inflammation and corticosteroid responsiveness; higher in T2-high asthma and CRSwNP	Non-invasive; endorsed in asthma guidelines [95]
Periostin	Serum, nasal tissue	Type 2 (IL-13-induced extracellular matrix remodeling)	Associated with eosinophilic airway remodeling and biologic responsiveness (anti-IL-13/IL-4Rα)	Biomarker for dupilumab and lebrikizumab trials [92]
Eosinophil cationic protein (ECP)	Serum, nasal lavage	Type 2 (eosinophil activation)	Reflects eosinophil degranulation and correlates with nasal polyp activity	Emerging biomarker for disease monitoring [93]
Total and allergen-specific IgE	Serum	Atopic/T2-high	Indicates allergic sensitization; predicts anti-IgE (omalizumab) response	Established diagnostic and therapeutic biomarker [96]
TARC/CCL17	Serum, nasal secretions	Type 2/Th2 chemokine axis	Correlates with AD + asthma comorbidity and CRS disease activity	Potential marker for unified airway inflammation [97]
IL-5, IL-13, IL-33, TSLP (local cytokines)	Nasal lavage, induced sputum	Type 2 epithelial alarmin response	Local cytokine levels correlate with severity, recurrence, and biologic response	Valuable for mechanistic and translational studies [54]
IL-17A, IFN-γ, TNF-α	Nasal tissue, BAL, serum	Non-T2 (Th1/Th17-dominant)	Associated with T2-low, neutrophilic, steroid-insensitive disease; potential biomarker for alternative therapies	Distinguishes endotypes unresponsive to biologics [98]
Filaggrin (FLG) mutations	Genomic DNA (buccal or blood)	Barrier dysfunction endotype	Associated with AD and CRS-asthma comorbidity; suggests epithelial barrier vulnerability	Genetic biomarker for the atopic march phenotype [99]
Microbiome dysbiosis (loss of diversity, *S. aureus* enrichment)	Nasal swab, sputum	Type 2 and mixed inflammatory endotypes	Correlates with local inflammation, IL-5 upregulation, and recurrence risk	Promising for endotype stratification and relapse prediction [99]
Transcriptomic signatures (ILC2, Th2, IL-33/TSLP module)	Nasal tissue, BAL	Type 2 immune network	Predicts biologic responsiveness and local disease activity	Emerging in RNA-seq-based Endotyping [100]
Composite multi-omics panels	Integrated (blood + nasal tissue + sputum)	Multi-endotype (T2-high, T2-low, mixed)	Improve predictive modeling for treatment response and relapse	Under validation; supports AI-based stratification [94]

Biomarkers span systemic (e.g., blood eosinophils, serum periostin) and local (e.g., nasal cytokines, microbiome signatures) compartments, reflecting the endotypic diversity of unified airway disease. Type 2 (T2-high) inflammation is characterized by IL-4, IL-5, IL-13, and epithelial alarmins (TSLP, IL-33), whereas non-T2 (T2-low) endotypes exhibit neutrophilic or Th17-dominant patterns. Integrating molecular, genomic, and microbiome-derived biomarkers with clinical phenotypes may enable precision stratification and biologic therapy selection across the upper and lower airway continuum. T2, type 2; Non-T2, non-type 2; CRSwNP, CRS with nasal polyps; TARC, thymus and activation-regulated chemokine; AD, atopic dermatitis; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor alpha; BAL, bronchoalveolar lavage.

Molecular Signatures for Endotype-Based Stratification

Molecular profiling advancements have reached a point where scientists can now identify distinct endotypes that exist in various allergic diseases. The T2-high endotype shows its distinct features through eosinophilia and increased FeNO levels, IL-4, IL-13, and IL-5 protein expression, while the T2-low endotype exhibits Th1 and Th17 dominant traits together with neutrophilic inflammation and elevated IL-17 and IFN-γ levels [54,108]. The molecular signatures of the disease serve two functions: they identify different disease patterns, and they help determine which treatments will succeed. The patients who show high levels of eosinophils and FeNO will experience positive results from anti-IL-5 treatments of mepolizumab and benralizumab and from anti-IL-1Rα treatment of dupilumab, whereas T2-low subtypes will respond to future anti-IL-17 and anti-TSLP treatment methods. Genetic and transcriptomic studies have discovered polymorphisms located in IL-4, IL-13, IL-33, and TSLP, which increase the risk of developing both asthma and CRS, while mutations in filaggrin (FLG) create a specific group of atopic dermatitis asthma comorbidity that occurs within the “atopic march” pattern [54,109]. These molecular understandings meld together, underscoring an endotype-based patient stratification process that enables clinicians to realign therapeutic interventions with individual inflammatory profiles.

Multi-Omics Integration and AI-Driven Precision Medicine

The development of multi-omics technologies, which include genomics, transcriptomics, proteomics, metabolomics, and microbiomics, has enabled researchers to shift their management approach from phenotype-based methods toward endotype-driven methods for treating CRS-asthma comorbidity [94,95]. Research studies in respiratory medicine and oncology show that integrated multi-omics profiling provides reliable methods for disease classification, biomarker identification, and treatment response prediction in complicated inflammatory diseases [110–112]. The study used transcriptomic analysis to examine nasal and bronchial tissues, which showed three specific gene expression patterns that matched type 2 inflammation, corticosteroid resistance, and biologic treatment response. The research team improved their biomarker panels through proteomic analysis of nasal secretions and serum, which helped them predict disease severity and recurrence risk after endoscopic sinus surgery. The studies on metabolomics and microbiomes demonstrate how metabolic pathways and microbial composition connect to different states of immune activation [113,114]. Artificial intelligence (AI) and machine-learning algorithms are increasingly used to combine high-dimensional datasets with clinical and imaging data. In other disease domains, radiogenomic models that merge computed tomography (CT) imaging data with molecular signatures have shown their ability to predict disease outcomes and classify diseases. AI-assisted image analysis has been successfully implemented in clinical settings through automatic polyp detection during colonoscopy and nodule characterization in lung imaging, which creates strong technical parallels for CRS applications [115]. The AI-driven frameworks of CRS-asthma comorbidity have developed biosignature composites that predict three outcomes: biologic response, postoperative recurrence, and exacerbation risk. The described methods create a direct connection between omics layers and clinical workflows through three specific applications, which include radiogenomics extraction of actionable features from sinus CT scans, transcriptomics and proteomics refinement of biomarker-guided patient selection, and microbiomics development of endotype-specific modulation strategies. The emerging clinical applications of these developments create a solid base for developing precision airway medicine according to the existing scientific advancements.

Therapeutic Strategies, Comparative Effectiveness, and Treatment Sequencing in CRS-Asthma Comorbidity

Chronic rhinosinusitis-asthma comorbidity represents a prototypical manifestation of unified airway disease, which requires integrated treatment approaches that treat common inflammatory pathways found in both upper and lower airways. The traditional treatment approach depends on the use of topical and systemic corticosteroids to achieve three goals, which include decreasing mucosal inflammation and eosinophil invasion while enhancing patient symptom management. The primary treatment for common respiratory disorders in patients with type 2-high CRS who have nasal polyps requires intranasal corticosteroids, which effectively decrease their nasal blockage and nasal polyps. Short courses of systemic corticosteroids are used only for severe diseases or acute disease exacerbations. The medication’s effectiveness for extended use is limited because it causes side effects, and patients with severe type 2 inflammation or mixed endotypes develop corticosteroid resistance [116,117]. Fig. 2 summarizes key cytokine cascades and alternative inflammatory pathways that represent potentially targetable mechanisms in chronic airway inflammation.

Endoscopic sinus surgery (ESS) remains essential for treating patients with CRS-asthma who do not respond to maximum medical treatment. ESS delivers significant symptom relief through its ability to restore sinus ventilation, enhance mucociliary clearance, and improve the topical drug delivery system. The procedure has consistently shown to provide parallel enhancements in asthma control, decreased asthma attacks, and reduced need for systemic corticosteroids [118,119]. Patients with asthma, aspirin-

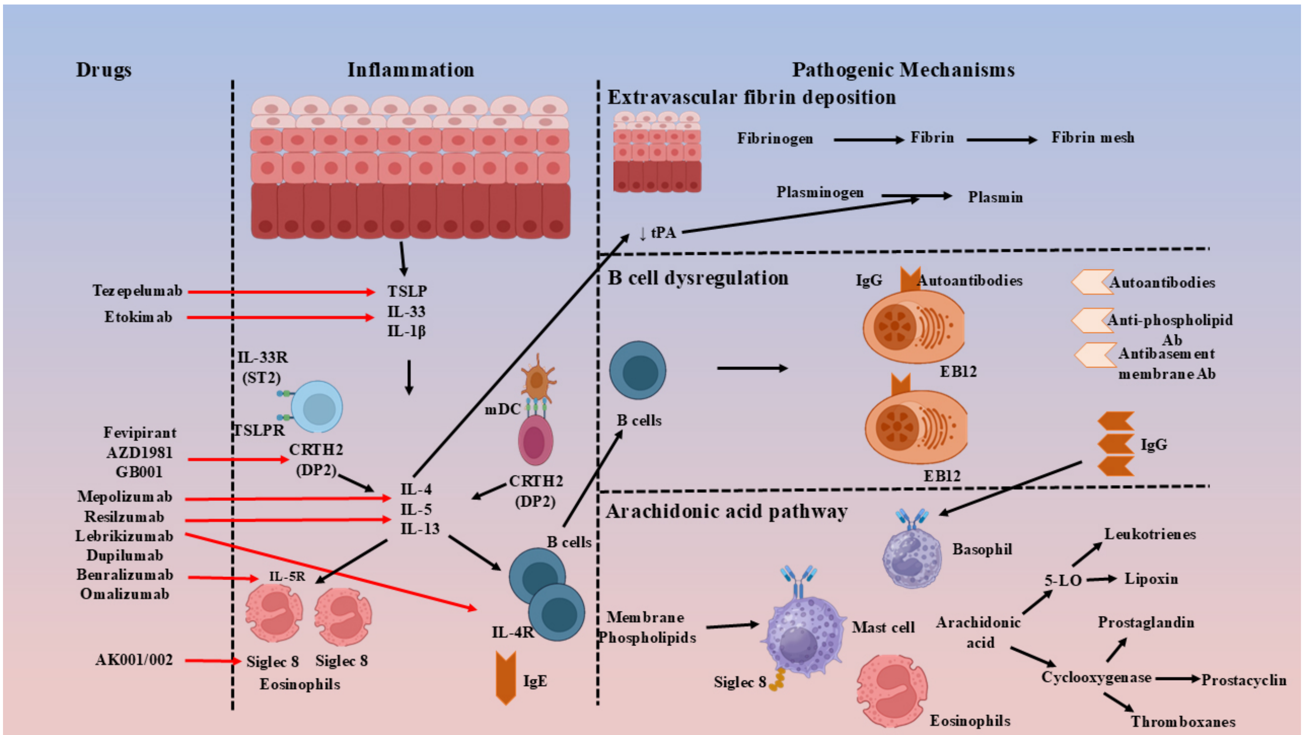

Fig. 2. Potentially targetable pathways in CRS and asthma. This schematic illustrates immunopathogenic pathways and therapeutic targets in chronic rhinosinusitis and asthma. Left panel: representative biologics and small-molecule agents directed against type 1 and type 2 cytokine signaling, those currently approved for CRSwNP or severe asthma, under active investigation, or with limited efficacy evidence. Central panel: the inflammation axis, highlighting epithelial alarmins (TSLP, IL-33), Th2 and ILC2 activation, and effector cytokines (IL-4, IL-5, IL-13) that drive eosinophilic inflammation, IgE production, and mucosal remodeling. Right panel: auxiliary mechanisms implicated in disease persistence, including coagulation-fibrin deposition, B-cell dysregulation, and arachidonic acid-mediated inflammation. Abbreviations: 5-LO, 5-lipoxygenase; mDC, myeloid dendritic cell; Siglec-8, sialic acid-binding Ig-like lectin 8; tPA, tissue plasminogen activator. The figure was created using Microsoft PowerPoint 2021 (Microsoft Corporation, Redmond, WA, USA) and Adobe Illustrator 2023 (Adobe Inc., San Jose, CA, USA).

exacerbated respiratory disease, or severe type 2 inflammation frequently exhibit persistent or recurrent disease activity, highlighting the limitations of surgery alone in managing the systemic inflammatory mechanisms underlying CRS. Recent developments in immunopathology research have established that CRS-asthma comorbidity exists as a collection of endotype-based disorders rather than single physical disorders. The new understanding of disease mechanisms has led to the creation of biologic treatments that specifically target essential type 2 cytokine signaling pathways [120–122]. Monoclonal antibodies which target IgE (omalizumab) and IL-5 and IL-5Rα (mepolizumab, reslizumab, and benralizumab) and IL-4Rα (dupilumab) have shown strong effectiveness to decrease nasal polyp size and enhance sinonasal symptoms and reduce asthma attacks and limit the need for systemic corticosteroids [123, 124]. Recently, durable and concurrent efficacy across the two compartments of sinuses and bronchial asthma has been clear for dupilumab, with the supportive claim of the "unified airway" theory of the therapy.

The combined use of two treatments together with their sequential application proves to be more effective than using either surgical procedures or biologic treatments as standalone options, according to results from comparative effectiveness studies. The combination of endoscopic sinus surgery and subsequent biologic treatment results in better symptom management and fewer need for revision surgeries and lasting quality-of-life benefits when compared to single treatment methods for patients who have severe type 2-high CRSwNP and uncontrolled asthma [125]. The presence of extensive lower airway damage together with systemic eosinophilia and frequent asthma attacks in patients, demonstrates that starting biologic treatment earlier leads to better results, which include both airway stabilization and reduced need for surgical procedures [126–128]. The research results demonstrate that ESS and biologics function as two separate treatment methods that treat specific physical blockages and two distinct types of immune system disorders.

An endotype-driven management algorithm forms a rational way for therapeutic choice and, ideally, sequencing [126]. Type 2-high disease, with its three symptoms of raised blood eosinophils and higher exhaled nitric oxide levels, and presence of IL-5 or periostin in tissues, demonstrates successful treatment outcomes with biologic medications that target type 2 disease mechanisms. The T2-low and mixed inflammatory endotypes show poor treatment outcomes with corticosteroids and existing biologic therapies because they primarily exhibit neutrophilic inflammation together with Th1 and Th17 signaling pathways [127–130]. In such cases, extended administration of low doses of macrolide antibiotics together with surgical outcome improvements and new treatment methods, which include epithelial alarmins TSLP, IL-33, IL-25, and their associated signaling pathways, JAK inhibitors, will provide effective treatment solutions.

The research currently investigates the best sequence for administering biological treatments to patients who require essential sleep study testing. Biologic treatment before surgery decreases mucosal swelling and surgical bleeding, whereas postoperative biologic treatment extends remission duration while decreasing recurrence probabilities. The current evidence supports a treatment approach that combines biomarker analysis with flexible scheduling to determine treatment times according to a patient's disease severity, their inflammatory status, and previous treatment results [131,132]. The high expenses of biologic therapies make cost-effectiveness assessments essential for clinical decision-making processes. ESS treatment remains affordable for most patients, but biologic therapy shows economic advantages because it decreases hospital stays, the use of systemic corticosteroids, and the need for additional surgical procedures in patients who have multi-compartment type 2 disease that does not respond to other treatments [133]. The combination of blood eosinophil counts together with FeNO measurements and postoperative recurrence risk assessment enables better patient selection, which leads to improved clinical results and efficient resource use. The new AI-based predictive systems show potential to enhance treatment pathways through their ability to combine clinical data with biomarker information and imaging results for personalized treatment decisions [133,134].

Future Direction and Research Gaps

Although scientists have made significant advancements in discovering type 2-driven inflammation mechanisms for chronic rhinosinusitis and asthma, they still lack a complete understanding of multiple mechanistic areas. The scientific community now identifies epithelial barrier dysfunction as the primary event that initiates disease progression because it enables allergens and microbes to invade the body, which leads to continuous inflammation [135,136]. The defective tight junctions of epithelial cells, together with activated innate immune systems and microbiome dysbiosis, create a research area that remains unknown. Current research shows that sinonasal microbiota serves as both an inflammation marker and an endotype-specific inflammation modifier, yet scientists have not established direct causal links. Sensory neurons, together with neuropeptides like substance P and CGRP, and local cytokine networks, establish neuroimmune connections that result in increased inflammation and worsened symptoms that include pain and hyperreactivity. The study of these interconnected barrier microbial-neural pathways will produce new therapeutic targets that will help develop combined treatment methods for CRS-asthma comorbidity.

Biologic treatments target IL-4Rα, IL-5, and IgE have revolutionized treatment for severe type 2 disease, yet actual medical practice still faces obstacles. The treatment requires annual expenses between USD 10,000 and 40,000, and it needs to be given through injections while patients experience ongoing inflammation that lasts more than one year, and their symptoms return after they stop treatment, which shows that they will probably need to continue receiving treatment for a long time [137]. The standard treatment path for CRS includes endoscopic sinus surgery, while other type 2 disorders use different treatment methods. Patients who undergo ESS experience greater polyp reduction compared to those who receive dupilumab treatment (nasal polyp score (NPS) –5.18 vs –4.27, $p < 0.02$), but biologic therapy provides better long-term results for scent ability and SNOT-22 assessment. The post-ESS recurrence rate shows wide variation, with 20–60% of patients experiencing recurrence within 4 years and 79% of patients experiencing recurrence within 12 years, which creates a need for predictive biomarkers that can determine which patients will gain the most from biologic therapy, surgery, or combination treatment. Economic modeling demonstrates that ESS provides greater cost efficiency than dupilumab when annual biologic expenses surpass USD 855 and revision surgery occurs. The use of biologic therapy after ESS helps decrease recurrence rates while improving long-term disease management, which requires extensive clinical research using unified airway endpoints through biomarker-driven trials (e.g., composite CRS-asthma control indices, airway cytokine profiles, and mucosal transcriptomics) [138,139].

Researchers can now use multi-omics technologies, which include genomics, transcriptomics, proteomics, metabolomics, and microbiomics, to study the different forms of CRS. The combination of these datasets with bioinformatics and AI tools enables researchers to predict endotypes and determine treatment response patterns while discovering medical biomarkers. Machine learning algorithms now identify transcriptomic signatures that can predict biological responses and post-surgical recurrence, yet their use in clinical settings has not advanced beyond early stages. The creation of AI-powered clinical decision tools that operate in real time and use omics data with specific patient clinical information will create a new standard for precise medical treatment. The establishment of standardized biobanks for CRS-asthma research requires researchers to work together and collect long-term samples, which will help validate their prediction models [56].

Research requires extensive time and multiple research sites to study complete CRS disease progression, treatment outcomes, and total airway inflammation development. The present clinical trials face restrictions because they use brief observation periods and different participant selection standards, and they do not have common testing requirements [140]. Future studies should include dynamic inflammation biomarkers, which include periostin, IL-5, and eosinophil cationic proteins, together with radiologic and functional measurements to enhance their abilities to predict patient relapse or remission. The most biologic trials currently exclude CRSsNP patients, yet recent findings show that certain non-type 2 or mixed endotypes can still gain advantages from specific therapeutic approaches. Researchers plan to create a connection between controlled trial results and actual medical practices by using broader patient selection criteria and endotype-based patient classification.

The shared medical mechanisms and treatment responses between CRS and asthma conditions create a strong justification for establishing combined airway treatment facilities. The multidisciplinary centres that combine otolaryngology, pulmonology, allergy-immunology, and clinical pharmacology will enable unified medical teams to perform patient evaluation, biomarker testing, and treatment planning [97,141]. The collaborative frameworks will improve patient selection for biologics and enable monitoring across upper and lower airway compartments, and establish shared decision-making that uses endotype-specific evidence. The use of unified airway care models will improve clinical outcomes and cost-effectiveness while speeding up the process of turning bench discoveries into precise therapeutic pathways.

Conclusions

CRS and asthma exemplify the concept of the unified airway, sharing overlapping immunologic mechanisms that drive disease expression across anatomical compartments. Recognition of common endotypes, particularly type 2-high inflammation, has enabled the development of targeted biologic therapies that improve outcomes in both upper and lower airway disease. At the same time, emerging non-type 2 mechanisms underscore the heterogeneity of CRS-asthma comorbidity and the limitations of phenotype-based management.

Integrated molecular diagnostics, validated biomarkers, and clinical metrics provide a foundation for precision medicine approaches that transcend traditional disease boundaries. Unified airway care models, supported by multidisciplinary collaboration, offer a practical framework for translating these advances into routine practice. These developments signal a shift from symptom-based treatment toward mechanism-driven, personalized management of CRS-asthma comorbidity.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors have made a significant contribution to the conceptualizations. The literature search was conducted by SM and YQG. SM has written, reviewed, and edited the original draft. YQG and JM have provided the resources and made essential changes to the manuscript. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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