

Review

Nasal Cytology as a Local Read-Out of Type 2 Inflammation and Epithelial Barrier Dysfunction in Chronic Rhinosinusitis with Nasal Polyps

Matteo Gelardi 

Unit of Otolaryngology, Department of Clinical and Experimental Medicine, University of Foggia, Viale Pinto 1, 71122 Foggia, Italy; matteo.gelardi@unifg.it

Abstract

Background: Chronic rhinosinusitis with nasal polyps, CRSwNP, represents one of the most clinically relevant models of type 2 inflammation in the upper airways. Its pathogenesis is not sustained by a single mechanism but by the continuous interaction between epithelial barrier damage, immune activation and tissue remodeling. Although several systemic biomarkers are currently used in clinical practice, they do not always reflect the inflammatory processes occurring directly within the sinonasal mucosa. **Objective:** This review discusses nasal cytology as a local and clinically accessible read-out of type 2 inflammation and epithelial barrier dysfunction in CRSwNP. Particular attention is given to the relationship between cytological patterns, underlying immune mechanisms and the use of biologic therapies. **Methods:** A narrative review of the literature was conducted, focusing on epithelial barrier abnormalities, type 2 inflammatory pathways, cytological phenotypes and available monoclonal antibodies. The clinical relevance of these elements was considered, with particular regard to patient stratification and therapeutic decision-making. **Results:** Epithelial barrier disruption promotes the release of alarmins such as TSLP, IL-25 and IL-33. These mediators activate both innate and adaptive type 2 immune responses and contribute to the persistence of mucosal inflammation. Nasal cytology allows direct assessment of the local inflammatory infiltrate and makes it possible to identify eosinophilic, mast cell-predominant and mixed eosinophil–mast cell patterns. These profiles appear to mirror different inflammatory settings. In particular, the coexistence of eosinophils and mast cells may identify patients with more severe, persistent or recurrent disease. When integrated into clinical tools such as clinical–cytological grading (CCG), nasal cytology may improve disease stratification, support follow-up and help orient biologic therapy according to the level of the inflammatory cascade predominantly involved. These cytological profiles may also support biologic treatment selection, therapeutic monitoring, and future tapering strategies by reflecting the predominant inflammatory pathway active at the mucosal level. **Conclusions:** Nasal cytology is a direct, reproducible and clinically useful approach for evaluating local inflammation in CRSwNP. By providing information from the mucosal site of disease, it complements systemic biomarkers and may support personalized therapeutic strategies and biologic treatment selection in CRSwNP.



Academic Editor: Nejat Düzgüneş

Received: 8 May 2026

Revised: 30 June 2026

Accepted: 6 July 2026

Published: 10 July 2026

Copyright: © 2026 by the author.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

Keywords: nasal cytology; type 2 inflammation; CRSwNP; epithelial barrier dysfunction; eosinophils; mast cells; biologic therapies; endotypes; precision medicine

1. Introduction

Chronic rhinosinusitis with nasal polyps, CRSwNP, is widely regarded as one of the most representative clinical expressions of type 2 inflammation in the upper airways. Its pathogenesis involves epithelial dysfunction, innate and adaptive immune responses, and tissue remodeling, which do not act as isolated events but as interconnected components of the same inflammatory process [1]. Among these elements, epithelial barrier impairment has received increasing attention, as it appears to play a decisive role not only in disease onset but also in its persistence over time [2,3].

The sinonasal epithelium is not simply a passive surface exposed to external stimuli. It is an active immunological interface that regulates the interaction between the host and the environment. When epithelial integrity is compromised and tight junctions are disrupted, allergens, pollutants and microbial products can more easily penetrate the mucosa. This favors immune activation and contributes to the maintenance of chronic inflammation [2]. For this reason, epithelial barrier dysfunction should not be considered merely the result of inflammation. In many respects, it represents one of the mechanisms through which inflammation is initiated, amplified and maintained [3].

A central step in this process is the release of epithelial-derived alarmins, including TSLP, IL-25 and IL-33. These mediators are produced in response to epithelial stress, microbial signals and environmental exposures, and they act as early amplifiers of type 2 inflammation [4,5]. Through the activation of group 2 innate lymphoid cells, ILC2s, and Th2 lymphocytes, they promote the production of cytokines such as IL-5 and IL-13, thereby linking epithelial injury with immune dysregulation [4–6]. This reciprocal relationship between barrier damage and immune activation is one of the reasons why CRSwNP often behaves as a chronic, relapsing and difficult-to-control disease.

The introduction of monoclonal antibodies targeting type 2 inflammatory pathways has profoundly changed the management of CRSwNP [7–9]. These treatments have confirmed the central role of type 2 inflammation and have made endotype identification increasingly relevant in routine clinical practice [7]. As a consequence, stratifying patients according to their inflammatory profile is no longer a purely academic exercise but a practical requirement for appropriate therapeutic planning.

Nevertheless, the biomarkers most commonly used in clinical practice still rely mainly on systemic measurements, including peripheral blood eosinophils, total IgE and circulating inflammatory mediators. These parameters are useful and remain important, but they provide only an indirect picture of a disease process that primarily develops within the sinonasal mucosa. In some patients, systemic markers and local inflammation may not overlap perfectly, which can complicate both prognostic assessment and therapeutic decisions.

Nasal cytology offers a simple, non-invasive and repeatable way to address this limitation. By allowing direct observation of the inflammatory cells present in the nasal mucosa, it provides real-time information on the local inflammatory environment. Eosinophilic, neutrophilic, mast cell-predominant and mixed patterns can be identified, and each of these profiles may correspond to a different pathogenic background.

Particular interest has recently focused on the coexistence of eosinophils and mast cells in the nasal mucosa. This observation suggests that CRSwNP cannot always be interpreted through a purely eosinophil-centered model. The interaction between eosinophils and mast cells may contribute to persistent inflammation, greater disease severity and increased risk of recurrence [10]. Nasal cytology is especially valuable in this regard because it makes this cellular interaction visible at the site where the disease actually occurs.

The incorporation of cytological findings into clinical tools such as clinical–cytological grading (CCG) has further strengthened the clinical relevance of nasal cytology. By connecting cellular patterns with disease severity, comorbidities and outcomes, CCG offers

a more structured interpretation of inflammatory heterogeneity. This is particularly important in the current therapeutic landscape, where biologic treatments require a careful understanding of the inflammatory mechanisms driving disease in each patient.

For these reasons, nasal cytology can be considered a local read-out of type 2 inflammation and epithelial barrier dysfunction in CRSwNP. It provides a practical bridge between immunological mechanisms and clinical decision-making, helping to move disease assessment toward a more individualized and biologically informed approach, with potential implications for therapeutic stratification, biologic treatment selection, longitudinal monitoring of response, and the possible identification of patients suitable for future tapering strategies.

2. Type 2 Inflammation and Biologic Therapeutic Pathways

Type 2 inflammation is the predominant inflammatory endotype in a substantial proportion of patients with CRSwNP. It arises from a complex interaction between epithelial barrier dysfunction, innate immune activation, adaptive Th2 responses and a cytokine network mainly driven by IL-4, IL-5 and IL-13 [7,11].

The process often begins at the epithelial level. In response to environmental triggers, microbial products or mechanical and inflammatory stress, epithelial cells release alarmins such as TSLP, IL-25 and IL-33 [4,5]. These molecules act upstream in the inflammatory cascade and are able to activate type 2 responses even before a fully antigen-driven adaptive immune response has developed. In particular, they stimulate ILC2s, which rapidly produce IL-5 and IL-13 and thereby promote eosinophilic inflammation [11,12].

At the same time, Th2 lymphocytes contribute to the persistence and organization of the inflammatory response through antigen-dependent mechanisms. The coexistence of innate and adaptive immune activation is a key feature of CRSwNP and may help explain the clinical variability observed among patients. Individuals with similar systemic biomarker profiles may show different disease severity, recurrence patterns or responses to therapy, suggesting that local inflammatory mechanisms are often more complex than systemic markers alone can indicate.

Within this cytokine environment, IL-5 plays a major role in eosinophil differentiation, recruitment and survival. IL-4 and IL-13, on the other hand, are involved in several additional features of the disease, including IgE class switching, mucus production, epithelial remodeling and barrier dysfunction [7,11]. Eosinophils are therefore central effector cells in CRSwNP. Through the release of cytotoxic granule proteins and extracellular traps, they contribute to tissue injury, mucus changes and amplification of local inflammation [13].

However, an exclusively eosinophil-centered interpretation of CRSwNP is probably insufficient. Mast cells are increasingly recognized as active participants in the type 2 inflammatory network. By releasing proteases, cytokines and lipid mediators, they can sustain inflammation, influence tissue remodeling and interact closely with eosinophils [10]. This interaction may create a local amplification loop, particularly in patients with persistent or recurrent disease.

The availability of monoclonal antibodies has made these pathways therapeutically relevant. Anti-IL-5 agents mainly target eosinophil survival and activity, while therapies directed against IL-4 and IL-13 signaling have broader effects on type 2 inflammation, including IgE-related mechanisms, mucus hypersecretion and epithelial dysfunction [7–9,11].

Despite these advances, responses to biologic therapies are not uniform. Some patients show marked clinical improvement, whereas others respond only partially or inconsistently. This variability suggests that systemic biomarkers may not always identify the dominant inflammatory pathway in an individual patient. A direct assessment of the local mucosal inflammatory profile may therefore provide additional and clinically meaningful information.

3. Nasal Cytology: Technique and Standardization

Nasal cytology is a non-invasive technique that allows direct examination of the cellular components involved in nasal inflammation. Initially considered mainly a descriptive method, it is now increasingly recognized as a reproducible and clinically informative tool [14].

Sampling is generally performed by gently scraping the middle portion of the inferior turbinate with a dedicated device, such as Nasal Scraping[®]. The procedure is simple, rapid and well tolerated. In most cases it can be performed in a few seconds and does not cause relevant discomfort to the patient. The collected material is then placed on a glass slide, air-dried and stained for microscopic evaluation.

May–Grünwald–Giemsa staining remains the reference method for routine nasal cytology. It allows reliable identification of eosinophils, neutrophils, lymphocytes, mast cells and epithelial alterations. When the staining is properly performed, it also provides useful information on cellular activation and degranulation, which may have important clinical implications [14].

Technical standardization is essential. Small differences in fixation, staining time, dilution or slide preparation can affect the quality of the sample and influence interpretation. For this reason, the use of standardized protocols is important both in clinical practice and in research. A slow May–Grünwald–Giemsa protocol, derived from hematological practice, may improve morphological definition and provide more consistent staining results [14].

An important contribution to this field has recently come from the Delphi consensus promoted by AICNA. This consensus has provided a structured methodological framework aimed at improving reproducibility, reducing interobserver variability and supporting a more uniform use of nasal cytology across different clinical and research settings [15].

One of the most relevant practical advantages of nasal cytology is its repeatability. Since the procedure is minimally invasive, it can be performed at different time points and used to monitor changes in the inflammatory infiltrate over time. This is particularly useful during follow-up or after the introduction of medical or biologic therapies. In some cases, modifications in the cytological pattern may be observed before a clear clinical response becomes evident.

4. Cytological Endotypes and Immunological Correlates

Nasal cytology allows the identification of different inflammatory patterns that may correspond, at least in part, to distinct immunological endotypes. Its value lies not only in counting inflammatory cells but in providing a direct view of the cellular microenvironment of the nasal mucosa [14].

Among the classical cytological phenotypes are non-allergic rhinitis with eosinophilia syndrome (NARES), non-allergic rhinitis with mast cells (NARMA), and non-allergic rhinitis with eosinophils and mast cells (NARESMA). These entities are defined by their predominant cellular components and are thought to reflect different inflammatory mechanisms [14,16].

NARES is characterized by prominent eosinophilic infiltration and is generally associated with a type 2 inflammatory profile. NARMA, by contrast, is defined by mast cell predominance and may indicate inflammatory mechanisms that differ from, or partly overlap with, eosinophil-driven disease [10]. NARESMA represents a mixed eosinophil–mast cell pattern and is often associated with a more severe, persistent or difficult-to-control clinical course [16].

In routine practice, mixed cytological profiles are frequently encountered. Their recognition is clinically relevant because these patterns may identify patients in whom inflammation is sustained by more than one cellular pathway. This may explain why some patients show incomplete responses to treatments directed at a single inflammatory

component. In this sense, nasal cytology does not merely classify inflammation; it helps interpret its biological complexity [16].

The identification of cytological endotypes may therefore contribute to a more refined understanding of CRSwNP heterogeneity. This is particularly relevant in the era of biologic therapies, where treatment selection increasingly depends on recognizing the dominant inflammatory mechanism rather than relying only on clinical phenotype or systemic biomarkers.

5. Eosinophil–Mast Cell Interaction and Epithelial Barrier Dysfunction

Eosinophils have long been considered central effector cells in type 2 inflammation. In CRSwNP, however, they are unlikely to explain the entire biological and clinical spectrum of the disease on their own. Increasing attention has therefore been directed toward mast cells and, more specifically, toward their interaction with eosinophils within the nasal mucosa [10,16].

Mast cells are not passive bystanders in chronic inflammation. Through the release of proteases, cytokines, lipid mediators and growth factors, they contribute to inflammatory persistence, epithelial damage and tissue remodeling [10]. Their interaction with eosinophils appears to be bidirectional rather than simply additive. Together, these two cell populations may establish a local amplification loop that sustains inflammation and makes disease control more difficult [16].

From a mechanistic point of view, eosinophils can activate mast cells through mediators such as major basic protein, eosinophil cationic protein and several cytokines. Mast cells, in turn, release tryptase, chymase, interleukins and other mediators that promote eosinophil recruitment, survival and activation. This reciprocal communication may occur through both IgE-dependent and IgE-independent mechanisms, creating a local environment in which inflammation tends to perpetuate itself [10].

This cellular crosstalk also has consequences for the epithelial barrier. Cytotoxic eosinophil-derived proteins, together with mast cell proteases and inflammatory mediators, may damage epithelial structures and alter tight junction integrity. The result is increased mucosal permeability, which facilitates the penetration of allergens, pollutants and microbial products and further amplifies immune activation [2,10,17].

Epithelial barrier dysfunction is now recognized as a major pathogenic feature of CRSwNP. Structural epithelial alterations allow environmental agents to cross the mucosal surface and maintain chronic immune stimulation [17,18]. These abnormalities are also closely linked to mucus dysfunction and altered mucin properties, which contribute to the formation of dense secretions and mucus plugs [19].

Within this framework, inflammation and epithelial damage should not be viewed as separate processes. Barrier dysfunction promotes inflammation, while inflammatory mediators further damage the barrier. Nasal cytology captures the cellular consequences of this cycle. For this reason, it may be interpreted not only as a marker of type 2 inflammation but also as an indirect morphological expression of epithelial barrier impairment at the mucosal surface.

6. Clinical–Cytological Grading (CCG) as a Translational Tool

The clinical value of nasal cytology becomes particularly evident when cytological findings are integrated with clinical information. Clinical–cytological grading (CCG) was developed precisely for this purpose: to combine cellular patterns with relevant clinical variables and provide a more structured assessment of disease severity in CRSwNP [20].

CCG considers the inflammatory infiltrate identified by nasal cytology, including eosinophils, mast cells, neutrophils and mixed patterns, together with clinical elements

such as symptom burden, comorbidities and recurrence. Among comorbidities, particular attention is given to asthma, allergic sensitization and aspirin-exacerbated respiratory disease, all of which are closely associated with type 2 inflammation and may influence both severity and prognosis.

This integrated approach is often more informative than the separate evaluation of clinical features or laboratory values. A patient may have systemic biomarkers that appear only moderately altered, while nasal cytology reveals an intense local inflammatory infiltrate. Conversely, systemic abnormalities may not always correspond to the same degree of mucosal inflammation. CCG helps place these findings within a more coherent clinical framework.

One of the strengths of CCG is its ability to capture inflammatory complexity. Rather than reducing disease assessment to a single parameter, it takes into account the coexistence of different inflammatory components. Mixed eosinophil–mast cell patterns are generally associated with higher scores and tend to identify patients with more severe, recurrent or difficult-to-control disease [16,20]. This is particularly relevant after surgery, when recurrence risk is an important clinical concern.

Available evidence suggests that higher CCG values are associated with greater disease severity, increased symptom burden and a higher probability of recurrence after medical or surgical treatment [20]. From a practical point of view, this makes CCG useful for identifying patients who may require closer follow-up or more intensive therapeutic strategies.

CCG may also support therapeutic decision-making. By translating cytological findings into a structured clinical score, it can help identify patients in whom type 2 inflammation is particularly prominent. Eosinophil-dominant or mixed eosinophil–mast cell profiles may indicate that patients are more likely to benefit from biologic therapies targeting type 2 pathways [7–9,20].

The possibility of repeating nasal cytology over time adds further value. Longitudinal assessment allows clinicians to monitor changes in the inflammatory infiltrate and update the CCG during follow-up. In some cases, cytological improvement may precede symptom improvement, while in others, persistent cellular inflammation may reveal incomplete disease control despite apparent clinical benefit [21].

In this sense, CCG represents a translational tool. It connects microscopic findings with clinical management and allows nasal cytology to move beyond a descriptive role, becoming part of a more personalized approach to CRSwNP.

7. Morphological Expression of Type 2 Inflammation in Nasal Cytology

The molecular pathways involved in type 2 inflammation in CRSwNP have been extensively studied, particularly with regard to cytokine signaling, epithelial activation and effector cell function. These mechanisms, however, are not only biochemical events. They also produce morphological changes that can be observed directly at the mucosal level.

Eosinophil extracellular traps are a relevant example. These structures are now considered active contributors to inflammation rather than simple by-products of eosinophil activation. Their formation leads to the release of cytotoxic proteins and galectin-10 into the extracellular environment, where they may aggregate within mucus. In CRSwNP, this process has been associated with disease severity and recurrence [13].

From the perspective of nasal cytology, similar features have long been recognized in nasal secretions. Free eosinophilic granules, nuclear debris, dense mucin aggregates and Charcot–Leyden crystals represent a characteristic morphological pattern of intense eosinophil activation. These findings can now be interpreted in light of the molecular mechanisms that underlie extracellular trap formation and mucus remodeling [13].

Nasal cytology therefore offers a direct link between immunological mechanisms and their structural consequences. It does not simply show the presence or absence of inflammatory cells. It allows the observer to recognize patterns of activation, degranulation, extracellular aggregation and epithelial damage. These features are particularly evident in samples with mixed eosinophil–mast cell infiltrates, where signs of activation in both cell populations may coexist with mucus remodeling and epithelial injury.

Dense mucus plugs are increasingly recognized as a hallmark of type 2-driven airway inflammation [19]. Their cytological appearance may reflect the combined effects of eosinophil activation, altered mucin composition, epithelial injury and local inflammatory amplification. In this regard, cytology provides information that complements both systemic biomarkers and histological evaluation.

These morphological findings should also be interpreted in relation to epithelial barrier dysfunction. Cytotoxic proteins, extracellular traps and mast cell-derived proteases may contribute to epithelial injury and tight junction disruption. This increases mucosal permeability and facilitates further exposure to environmental agents, thereby maintaining the inflammatory cycle [17–19].

Thus, the cytological patterns observed in nasal secretions are not merely descriptive findings. They represent the visible expression of biological processes occurring at the disease site. While molecular studies identify the pathways involved, nasal cytology allows their downstream effects to be directly observed in clinical practice.

In this perspective, nasal cytology can be regarded as a cellular window into type 2 inflammation and epithelial dysfunction. It provides a real-time representation of the mucosal inflammatory environment and may offer additional insight into disease activity, severity and recurrence risk [13].

8. Implications for Targeted Biologic Therapy

Monoclonal antibodies have reshaped the management of CRSwNP by allowing targeted modulation of type 2 inflammatory pathways [7–9]. Their introduction has also made clear that CRSwNP is not a uniform disease. Evidence-based position papers and randomized controlled trials have shown that biologic therapies can reduce nasal polyp burden, improve symptoms and olfaction, and decrease the need for systemic corticosteroids or surgery in appropriately selected patients [22–26]. Clinical responses vary considerably, and this variability reflects the biological heterogeneity of the inflammatory mechanisms involved [8].

Currently available biologics act at different levels of the type 2 inflammatory cascade. Anti-IL-5 therapies primarily target eosinophil survival and activity, thereby acting on one of the main effector components of type 2 inflammation [27]. In contrast, blockade of IL-4 and IL-13 signaling has broader biological effects, including modulation of IgE-related mechanisms, mucus production and epithelial barrier function [7,28].

Anti-IgE therapy, represented by omalizumab, acts at the interface between adaptive immunity and effector cell activation. By reducing IgE-mediated stimulation of mast cells and basophils, it may be particularly relevant in patients in whom allergic mechanisms coexist with other inflammatory components [29]. Tezepelumab, by targeting TSLP, represents an upstream therapeutic strategy potentially capable of modulating both innate and adaptive immune responses [4,5,30].

These therapies can therefore be viewed as acting at different points along the same pathogenic continuum. This concept may help explain why patients with apparently similar clinical presentations do not always respond in the same way. In current practice, however, therapeutic decisions are still often guided by systemic biomarkers such as blood eosinophils and serum IgE. These markers are useful, but they do not always reflect the inflammatory profile within the nasal mucosa.

This is where nasal cytology may provide additional value. Directly evaluating the inflammatory infiltrate at the disease site may help identify the dominant cellular component in an individual patient. An eosinophil-dominant profile may support the rationale for anti-IL-5 therapy. A mixed eosinophil–mast cell pattern may suggest a broader type 2 inflammatory profile, potentially more consistent with strategies targeting IL-4 and IL-13 signaling. A mast cell-rich pattern, especially in the presence of IgE-related mechanisms, may raise the relevance of anti-IgE therapy.

Epithelial barrier dysfunction must also be considered in therapeutic reasoning. Since barrier impairment contributes to immune activation and inflammatory persistence, treatments that influence epithelial function and upstream cytokine signaling may have particular relevance in selected patients [17,18]. In this view, cytological assessment may help connect the clinical phenotype with the underlying inflammatory cascade.

The growing availability of biologics acting at different levels of type 2 inflammation makes a more precise characterization of local disease increasingly important. In patients with complex or mixed cytological profiles, nasal cytology may help explain partial responses, guide treatment selection and support follow-up during biologic therapy.

Although nasal cytology should not be considered a stand-alone tool for choosing biologic treatment, it can provide clinically meaningful information when interpreted together with symptoms, endoscopic findings, comorbidities and systemic biomarkers.

In clinical practice, the value of nasal cytology during biologic therapy may lie less in the selection of a single drug and more in the dynamic assessment of local inflammatory control. A reduction in eosinophils, mast cells or mixed eosinophil–mast cell infiltration during follow-up may indicate effective suppression of the dominant mucosal inflammatory pathway. Conversely, persistence of local cellular inflammation despite clinical improvement may suggest incomplete disease control and may support closer monitoring or therapeutic reassessment. From this perspective, repeated nasal cytology may provide additional information for longitudinal management, optimization of biologic treatment and, in selected stable patients, future tapering strategies.

To facilitate the translation of these concepts into clinical practice, the proposed relationship between nasal cytological phenotypes, inflammatory pathways and their potential therapeutic implications is summarized in Table 1.

Table 1. Proposed integration of nasal cytological phenotypes into precision medicine for chronic rhinosinusitis with nasal polyps (CRSwNP).

Nasal Cytological Phenotype	Predominant Inflammatory Pathways	Clinical Significance	Potential Implications for Biologic Therapy and Follow-Up
Eosinophil-predominant	IL-5, IL-4/IL-13, eosinophilic Type 2 inflammation	Associated with eosinophilic CRSwNP, increased tissue eosinophilia, severe disease and higher recurrence risk	Supports identification of patients with a predominant eosinophilic endotype; serial cytology may monitor eosinophil depletion during biologic treatment.

Table 1. Cont.

Nasal Cytological Phenotype	Predominant Inflammatory Pathways	Clinical Significance	Potential Implications for Biologic Therapy and Follow-Up
Mast cell-predominant	IgE-mediated activation, IL-4/IL-13	Persistent local inflammation, epithelial activation and mediator release	May identify patients with prominent mast-cell involvement; useful for evaluating changes in mast-cell infiltration during treatment.
Mixed eosinophil–mast cell phenotype (NARESMA-like)	IL-5, IL-4/IL-13, IgE, TSLP and epithelial alarmin activation	Highest inflammatory burden, epithelial barrier dysfunction, increased recurrence risk and more severe CRSwNP	Represents the cytological phenotype most closely associated with severe Type 2 inflammation; may support therapeutic stratification, longitudinal monitoring and future tapering strategies after sustained local inflammatory control.
Neutrophil-predominant	IL-17, IL-8, innate immune activation	Suggests non-Type 2 inflammation, possible bacterial colonization/biofilm and reduced responsiveness to current Type 2 biologics	May identify patients requiring alternative therapeutic approaches and further microbiological investigation rather than Type 2-targeted biologics.
Mixed or evolving phenotype	Overlapping Type 2, non-Type 2 and epithelial alarmin (TSLP) pathways	Dynamic inflammatory profile reflecting disease evolution or treatment-induced changes	Serial nasal cytology may document inflammatory shifts over time, complement systemic biomarkers and support personalized treatment optimization.

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; TSLP, thymic stromal lymphopoietin. The therapeutic implications reported are complementary to current guideline-based indications and should not be interpreted as stand-alone criteria for biologic selection.

Although this framework is primarily hypothesis-generating, it provides a practical model for integrating local cytological findings into precision medicine strategies for CRSwNP.

9. Future Perspectives

The role of nasal cytology is likely to expand as airway inflammatory diseases are increasingly approached through precision medicine. In this framework, nasal cytology has been proposed as an important tool for disease characterization and management [31]. Its future development will probably depend on the ability to combine direct cellular observation with more standardized, quantitative and technologically supported approaches.

Digital pathology and automated image analysis may improve reproducibility by supporting standardized interpretation of cytological slides. Automated recognition and quantification of inflammatory cells could reduce operator-dependent variability and facilitate more consistent evaluation across different centers. These tools could support more consistent interpretation of cytological slides across different centers and may help identify subtle

features that are sometimes difficult to recognize by visual assessment alone, such as early degranulation, low-grade mixed inflammation or extracellular aggregation [32,33].

Future applications will likely move beyond simple cell counting. Greater emphasis may be placed on the recognition of complex cytological patterns and functional signs of activation, including degranulation and extracellular trap formation. In this way, nasal cytology could evolve from a predominantly descriptive technique into a more functional interpretation of the local inflammatory milieu [13].

Another promising direction is the integration of cytology with omics-based approaches. Combining cellular findings with transcriptomic, proteomic or metabolomic data may offer a more comprehensive characterization of airway inflammation. Such integration could help identify new biomarkers and improve the relationship between local inflammatory patterns and clinical outcomes [34,35].

From a practical standpoint, nasal cytology may also become more accessible in point-of-care settings. Simplified protocols, standardized staining procedures and digital support could facilitate its use in routine clinical practice. This would be particularly useful in settings where rapid assessment of local inflammation may influence therapeutic decisions.

Longitudinal monitoring during biologic therapy is another area of growing interest. In patients receiving biologic therapies, repeated cytological assessment may help detect early signs of response or reveal persistent local inflammation despite apparent clinical improvement [21,36]. This could be especially relevant in patients with recurrent disease or mixed inflammatory profiles.

Finally, the potential application of nasal cytology extends beyond CRSwNP. Its use in other inflammatory airway disorders may support the concept of the unified airway and contribute to a more integrated assessment of upper and lower airway inflammation [14].

10. Conclusions

CRSwNP is a biologically heterogeneous disease in which local immune mechanisms and epithelial barrier dysfunction play a central role. This complexity is not always adequately captured by systemic biomarkers alone. Although circulating markers remain useful in clinical practice, they often provide only a partial view of the inflammatory processes occurring within the sinonasal mucosa.

Nasal cytology offers a direct and clinically meaningful method for assessing inflammation at the site of disease. By directly reflecting the cellular environment of the nasal mucosa, it complements systemic biomarkers and allows a more accurate interpretation of the patient's inflammatory profile.

The recognition of specific cytological patterns, particularly mixed eosinophil–mast cell infiltrates, may improve the understanding of disease severity, persistence and recurrence. It may also help clinicians interpret heterogeneous or incomplete responses to treatment.

When integrated with clinical evaluation, comorbidities, endoscopic findings and systemic biomarkers, nasal cytology moves beyond a purely descriptive role. It becomes integrated into therapeutic reasoning and patient stratification, linking local inflammatory patterns with precision medicine approaches in CRSwNP.

From this perspective, nasal cytology can be considered a local read-out of type 2 inflammation and epithelial barrier dysfunction, linking cellular findings with the pathogenic mechanisms that sustain CRSwNP [17,18]. In the era of biologic therapies and precision medicine, direct evaluation of the mucosal inflammatory environment may provide a more biologically grounded approach to airway inflammatory disease.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Yang, C.; Guo, L.; Wang, Y.; Jiang, W.; Chen, S.; Gu, Q. The advance on pathophysiological mechanisms of type 2 chronic rhinosinusitis with nasal polyposis. *Front. Allergy* **2025**, *6*, 1599797. [\[CrossRef\]](#)
2. Klimek, L.; Becker, S.; Haxel, B.; Cuevas, M.; Huber, P.; Chaker, A.; Pfaar, O.; Laudien, M.; Beutner, C.; Hagemann, J.; et al. Different immunological types of CRSwNP in the context of the new European EAACI nomenclature. Part 2: Hypersensitivity reactions of type V, epithelial barrier defects. *HNO* **2025**, *74*, 174–182. [\[CrossRef\]](#)
3. Meng, J.; Xiao, H.; Xu, F.; She, X.; Liu, C.; Canonica, G.W. Systemic barrier dysfunction in type 2 inflammation diseases: Perspective in the skin, airways, and gastrointestinal tract. *Immunol. Res.* **2025**, *73*, 60. [\[CrossRef\]](#)
4. Cheng, F.; Wang, Y.; Gao, Y.; Zhang, C.; Zhang, Q.; Chen, J.; Zhou, Y.; Shi, L.; Hu, L.; Wang, H.; et al. Current understanding of epithelial-derived alarmins in chronic rhinosinusitis with nasal polyps. *Clin. Rev. Allergy Immunol.* **2025**, *68*, 59. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Peters, A.T.; Han, J.K.; Heffler, E.; McClenahan, F.; Caveney, S.; Le, T.T.; Zhou, Y.; Shi, L.; Hu, L.; Wang, H.; et al. Thymic stromal lymphopoietin as a therapeutic target in patients with chronic rhinosinusitis and nasal polyps. *Clin. Exp. Immunol.* **2025**, *219*, uxaf041. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Chiu, J.; Fastenberg, J.; Tong, C.; Navetta-Modrov, B.; Marcus, S. Biologics for chronic rhinosinusitis with nasal polyposis: Current landscape and future directions. *Laryngoscope Investig. Otolaryngol.* **2025**, *10*, e70282. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Bachert, C.; Hicks, A.; Gane, S.; Peters, A.T.; Gevaert, P.; Nash, S.; Zhou, Y.; Shi, L.; Hu, L.; Wang, H.; et al. The interleukin-4/interleukin-13 pathway in type 2 inflammation in chronic rhinosinusitis with nasal polyps. *Front. Immunol.* **2024**, *15*, 1356298. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Bagnasco, D.; Brussino, L.; Biagini, C.; Cosmi, L.; De Corso, E.; La Mantia, I.; Zhou, Y.; Shi, L.; Hu, L.; Wang, H.; et al. Management of patients with chronic rhinosinusitis with nasal polyps (CRSwNP): Results from a survey among allergists and clinical immunologists and otorhinolaryngologists. *World Allergy Organ. J.* **2024**, *17*, 100895. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Di, Y.; Zeng, R.; Huang, L.; Wu, Y.; Wu, Q. Advance in biologics for chronic rhinosinusitis with nasal polyps. *Front. Allergy* **2026**, *7*, 1759649. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Locatello, L.G.; Tonon, S.; Mele, V.; Santini, S.; Miani, C.; Pucillo, C.E.M. Update on the biological and clinical relevance of mast cells in chronic rhinosinusitis with nasal polyps. *Biomedicines* **2024**, *12*, 2647. [\[CrossRef\]](#) [\[PubMed\]](#)
11. AlBloushi, S.; Al-Ahmad, M. Exploring the immunopathology of type 2 inflammatory airway diseases. *Front. Immunol.* **2024**, *15*, 1285598. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Xing, Z.; Liu, S.; He, X. Critical and diverse role of alarmin cytokines in parasitic infections. *Front. Cell Infect. Microbiol.* **2024**, *15*, 1285598. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Chen, C.; Li, H.; Hou, Y.; Wen, Y.; Li, J.; Zhong, H.; Lu, T.; Li, Z.; Sun, L.; Lai, S.; et al. Prognostic significance of eosinophil extracellular traps in chronic rhinosinusitis and innovative nanosheets-based clearance therapy. *Clin. Exp. Allergy* **2026**, *56*, 650–664. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Heffler, E.; Landi, M.; Caruso, C.; Fichera, S.; Gani, F.; Guida, G.; Liuzzo, M.T.; Pistorio, M.P.; Pizzimenti, S.; Riccio, A.M.; et al. Nasal cytology: Methodology with application to clinical practice and research. *Clin. Exp. Allergy* **2018**, *48*, 1092–1106. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Macchi, A.; Gelardi, M.; Landi, M.; Gramellini, G.; Giancaspro, R.; Nappi, L.; Imperatore, C.; Bocciolini, C.; Seccia, V.; Pecoraro, P.; et al. Standardization of nasal cytology: An expert-based Delphi consensus. *Curr. Allergy Asthma Rep.* **2026**, *26*, 15. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Gelardi, M.; Giancaspro, R.; Duda, L.; Quaranta, V.N.; Pizzulli, C.; Maiorano, E.; Di Canio, F.M.; Ruzza, A.; Iannuzzi, L.; Quaranta, N.A.A.; et al. Eosinophil–mast cell pattern of intraepithelial infiltration as a marker of severity in chronic rhinosinusitis with nasal polyps. *Sci. Rep.* **2023**, *13*, 12101. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Huang, Z.Q.; Liu, J.; Sun, L.Y.; Ong, H.H.; Ye, J.; Xu, Y.; Wang, D.Y. Updated epithelial barrier dysfunction in chronic rhinosinusitis: Targeting pathophysiology and treatment response of tight junctions. *Allergy* **2024**, *79*, 1146–1165. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Petalas, K.; Goudakos, J.; Konstantinou, G.N. Targeting epithelium dysfunction and impaired nasal biofilms to treat immunological, functional, and structural abnormalities of chronic rhinosinusitis. *Int. J. Mol. Sci.* **2023**, *24*, 12379. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Fahy, J.V.; Dickey, B.F. Airway mucus function and dysfunction. *N. Engl. J. Med.* **2010**, *363*, 2233–2247. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Gelardi, M.; Fiorella, R.; Fiorella, M.L.; Russo, C.; Soleti, P.; Ciprandi, G. Nasal-sinus polyposis: Clinical cytological grading and prognostic index of relapse. *J. Biol. Regul. Homeost. Agents* **2009**, *23*, 181–188. [\[PubMed\]](#)

21. Gelardi, M.; Giancaspro, R.; Quaranta, V.N.; La Gatta, E.; Ruzza, A.; Cassano, M. Dupilumab's impact on nasal cytology: Real life experience after 1 year of treatment. *Am. J. Otolaryngol.* **2024**, *45*, 104275. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Fokkens, W.J.; Lund, V.J.; Hopkins, C.; Hellings, P.W.; Kern, R.; Reitsma, S.; Toppila-Salmi, S.; Bernal-Sprekelsen, M.; Mullol, J.; Alobid, I.; et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* **2020**, *58*, 1–464. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Bachert, C.; Han, J.K.; Desrosiers, M.; Hellings, P.W.; Amin, N.; Lee, S.E.; Mullol, J.; Greos, L.S.; Bosso, J.V.; Laidlaw, T.M.; et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps, LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52: Results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* **2019**, *394*, 1638–1650. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Han, J.K.; Bachert, C.; Fokkens, W.J.; Desrosiers, M.; Wagenmann, M.; Lee, S.E.; Smith, S.G.; Martin, N.; Mayer, B.; Yancey, S.W.; et al. Mepolizumab for chronic rhinosinusitis with nasal polyps, SYNAPSE: A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir. Med.* **2021**, *9*, 1141–1153. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Gevaert, P.; Omachi, T.A.; Corren, J.; Mullol, J.; Han, J.; Lee, S.E.; Kaufman, D.; Ligueros-Saylan, M.; Howard, M.; Zhu, R.; et al. Efficacy and safety of omalizumab in nasal polyposis: Two randomized phase 3 trials. *J. Allergy Clin. Immunol.* **2020**, *146*, 595–605. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Bachert, C.; Mannent, L.; Naclerio, R.M.; Mullol, J.; Ferguson, B.J.; Gevaert, P.; Hellings, P.; Jiao, L.; Wang, L.; Evans, R.R.; et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: A randomized clinical trial. *JAMA* **2016**, *315*, 469–479. [\[CrossRef\]](#) [\[PubMed\]](#)
27. McCann, M.R.; Kosloski, M.P.; Xu, C.; Davis, J.D.; Kamal, M.A. Dupilumab: Mechanism of action, clinical, and translational science. *Clin. Transl. Sci.* **2024**, *17*, e13899. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Gyawali, B.; Georas, S.N.; Khurana, S. Biologics in severe asthma: A state-of-the-art review. *Eur. Respir. Rev.* **2025**, *34*, 240088. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Sindher, S.B.; Hillier, C.; Anderson, B.; Long, A.; Chinthrajah, R.S. Treatment of food allergy: Oral immunotherapy, biologics and beyond. *Ann. Allergy Asthma Immunol.* **2023**, *131*, 29–36. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Tondina, E.; Codazzi, A.C.; Castorina, R.; Di Micco, R.; Dutto, C.; Leoncini Bartoli, L.; Lepore, G.; Marseglia, G.L.; Brambilla, I. Biologic therapies for severe pediatric asthma: Efficacy, safety, and biomarker-guided selection. *Front. Allergy* **2026**, *7*, 1757445. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Zhang, Y.; Zhang, L. Nasal cytology: Cornerstone and future directions in precision nasal disease management. *Asia Pac. Allergy* **2025**, *15*, 245–246. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Zhang, X.; Xu, X.; Liu, W.; Qin, L.; Song, Y.; Li, J.; Xi, L.; Wang, C.; Zhang, L.; Zhang, Y. Development of artificial intelligence for quantitative assessment of nasal inflammatory cytology in chronic rhinitis by whole-slide images. *Int. Forum Allergy Rhinol.* **2025**, *16*, 272–282. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Desolda, G.; Dimauro, G.; Esposito, A.; Lanzilotti, R.; Matera, M.; Zancanaro, M. A human–AI interaction paradigm and its application to rhinocytology. *Artif. Intell. Med.* **2024**, *155*, 102933. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Szczesny, B.; Boorgula, M.P.; Chavan, S.; Campbell, M.; Johnson, R.K.; Kammers, K.; Thompson, E.E.; Cox, M.S.; Shankar, G.; Cox, C.; et al. Multi-omics in nasal epithelium reveals three axes of dysregulation for asthma risk. *Nat. Commun.* **2024**, *15*, 4546. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Poole, A.; Urbanek, C.; Eng, C.; Schageman, J.; Jacobson, S.; O'Connor, B.P.; Galanter, J.M.; Gignoux, C.R.; Roth, L.A.; Kumar, R.; et al. Dissecting childhood asthma with nasal transcriptomics distinguishes subphenotypes of disease. *J. Allergy Clin. Immunol.* **2014**, *133*, 670–678. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Piatti, G.; Battilocchi, L.; Cozzi, A.; Gaini, L.M.; Aldè, M.; Pignataro, L.; Torretta, S. Nasal cytology is useful for evaluating and monitoring the therapeutic response to biologics in chronic rhinosinusitis with nasal polyposis. *Biomedicines* **2025**, *14*, 77. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.