Review article

CHRONIC RHINOSINUSITIS: TO WHAT EXTENT DOES ALLERGY PLAY A ROLE?

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ABSTRACT

Chronic rhinosinusitis (CRS) is a common and burdensome inflammatory disease of the nasal mucosa and paranasal sinuses that affects approximately 5–12% of the population worldwide. CRS can significantly impair productivity, reduce quality of life and place a substantial burden on healthcare systems globally. Whereas multiple factors contribute to its pathogenesis, the role of allergy in CRS remains a subject of ongoing debate. However, advances in the field of allergy pathophysiology and endotype-driven inflammation may lead to more precise management strategies in the future. This review examines the evidence linking allergic pathways to CRS, outlines pathophysiological mechanisms and discusses the diagnostic and therapeutic implications for clinical practice.

Keywords: chronic rhinosinusitis, epithelial dysfunction, Type 2 inflammation, allergy

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as inflammation of the nasal mucosa and paranasal sinuses that persists for more than 12 weeks, with the presence of two or more symptoms (one of which should be nasal blockage or nasal discharge): and/or facial pain/pressure and/or hyposmia.[1] The presence of a cough can be an additional symptom in a child.[1] It is a heterogenous disease and its aetiology reflects a complex interplay between bacterial, viral and fungal infections, environmental exposures and underlying host factors. This results in airway epithelial dysfunction, the activation of multiple immunological mechanisms, and chronic persistent inflammation.[2]

Traditionally, CRS has been divided into two main phenotypes on the basis of the presence or absence of nasal polyps: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP).[3] However, studies have shown that the underlying inflammation in both clinical entities is highly heterogenous and dependent on multiple other external and host factors, which renders the clinical relevance of this classification less important.[3] An allergy is defined as 'an unexpected abnormal or exaggerated reaction to an exogenous stimulus involving the immune system'.[4] Hypersensitivity is defined as 'an undesirable, uncomfortable or damaging response that arises from an overreaction of the adaptive immune response'.[4] Historically, hypersensitivity reactions were first described by Coombs and Gell[5] in 1968 and were divided into four categories: Type I – immediate (IgE-mediated), Type II – cytotoxic (antibody-mediated), Type III – immune-complex-mediated and Type IV – delayed type (T-cell-mediated).[5]

In 2023 the European Academy of Allergy and Clinical Immunology (EAACI) published a position paper in which it proposed an updated nomenclature of allergic diseases. This nomenclature classified hypersensitivity reactions into nine different types comprising antibody-mediated (I-III), cell-mediated (IVa-c), tissue-driven mechanisms (V-VI) and direct response to chemicals (VII).[4] Type I, IgE-dependent reactions, involves an initial sensitisation phase after exposure to an allergen: for example, pollens, house-dust mite (HDM), mould, animal dander, insect venoms, foods and drugs. Helper T-cells help B-cells to mature and produce high-affinity serum-specific IgE. The effector phase occurs on subsequent exposure to the same allergen, with the cross-linking of IgE antibodies resulting in mast-cell degranulation. The activation and migration of eosinophils contributes to the chronicity of the inflammatory response, which involves Type-IVb mechanisms. This reciprocal regulation of the Type-I and Type-IVb immune mechanisms plays a cardinal role in the development of allergy.[4] Advances in knowledge in the field of hypersensitivity and allergic diseases has led to the concept of endotype-driven thinking being formulated, where an understanding of the individual underlying immune responses can lead to the development of more sophisticated diagnostic tools, improved treatment strategies and better disease management – so called 'precision' and 'personalised' medicine.[4]

In CRS, the classification that better reflects the underlying pathophysiology is dependent on underlying endotypes. In CRSwNP and CRSsNP, three main endotypes – T1, T2 and T3, based on the elevation of T-cell cytokines Th1, Th2 and Th17 respectively – have been identified.[3] The role of IgE-mediated allergy in CRSwNP and CRSsNP continues to be controversial, with various studies showing conflicting results.[1] Whether Type-I IgE-mediated allergy drives CRS directly or merely exacerbates

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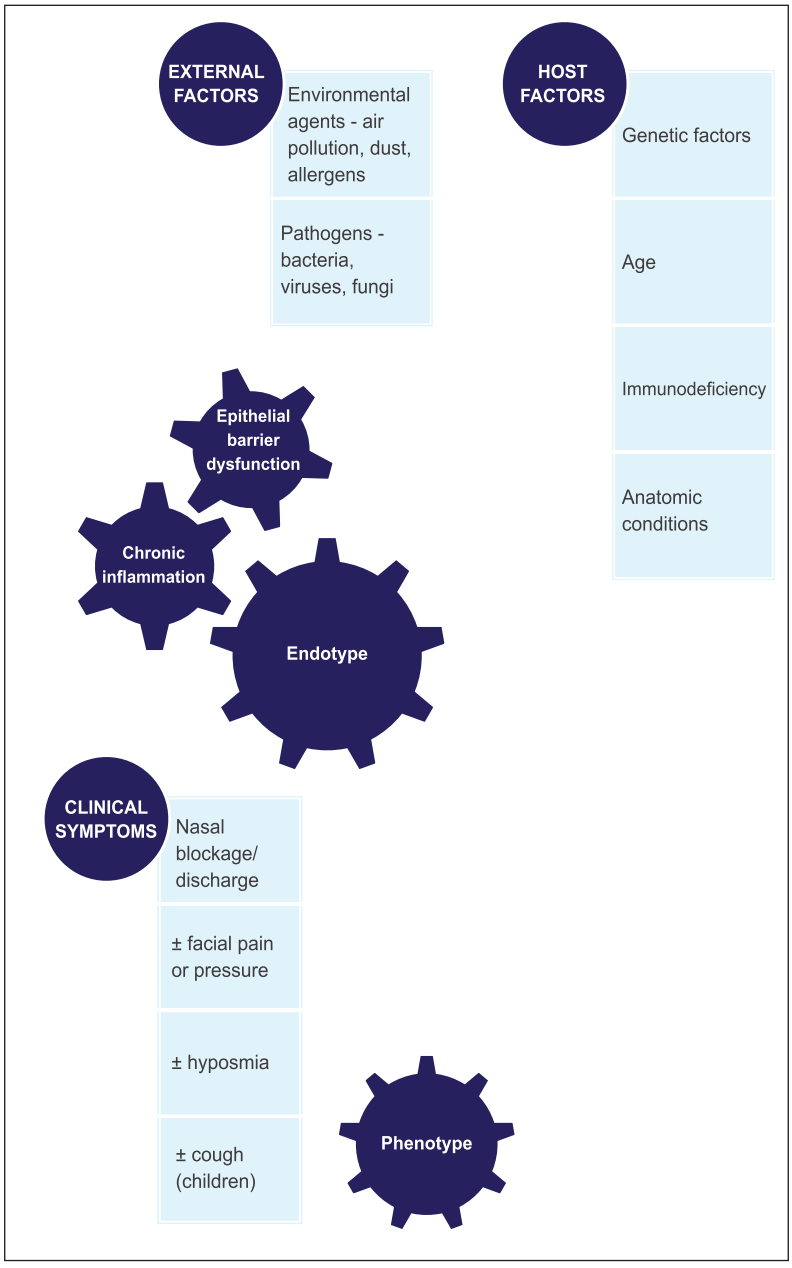

Figure 1: Aetiology and Pathogenesis of CRS (adapted from [1,2]).

symptoms in predisposed individuals remains an area of uncertainty. Recent literature reviews have shown a stronger association with allergy in different unique phenotypes of CRS, namely, central compartment atopic disease (CCAD) and allergic fungal rhinosinusitis (AFRS), more so than in CRSwNP and CRSsNP.[1,6]

AETIOLOGY AND PATHOGENESIS OF CRS

Several factors have been found to be associated with the onset and development of CRS. Geographical factors, exposure to various environmental agents (air pollution, dust and allergens), pathogens (bacterial, viral and fungal) and host factors (age, genetics, underlying immunodeficiency) can result in airway epithelium dysfunction.[1,3] Cystic fibrosis, primary ciliary dyskinesia and primary and secondary immunodeficiency syndromes are important co-morbid conditions associated with altered mucosal immunity and poor mucociliary clearance. These disorders are significant contributors to the pathogenesis of CRS.[1]

The innate immune system is activated to identify and eliminate pathogenic agents and to activate cells of the adaptive immune system through antigen presentation. Dysregulation of the innate and adaptive immune systems in patients with CRS leads to persistent chronic inflammation, resulting in clinical symptoms. 'Phenotype' refers to the clinically observable characteristics or traits of a disease whereas 'endotype' is a subtype of a disease, which is defined by distinct functional or pathobiological mechanisms.[7] When applied to CRS, the persistent inflammation of the sinonasal epithelium (either Type I, Type 2 or Type 3) is known as the endotype whereas the symptoms – including nasal blockage and/or discharge, facial pain/pressure and hyposmia with or without polyps – determine the phenotype.[1] The aetiology and pathogenesis of CRS is illustrated in Figure 1.

IMMUNOLOGY OF CRS

AIRWAY EPITHELIUM

External factors (allergens, pathogens and pollutants) trigger airway epithelial dysfunction by activating both the innate and the adaptive immune systems, hence the definitive shift in view of the sinonasal epithelium from a passive mechanical barrier to an immunologically active organ.[3] Airway epithelium dysfunction occurs through various mechanisms, including sinus microbiota dysbiosis, mucociliary clearance dysfunction, tight junction disruption and tissue remodelling (polyp formation, goblet cell hyperplasia).[2] The airway epithelium acts as a physical barrier and is the first line of defence in the sinuses. The mechanisms of defence include mucociliary clearance, the production of pro-inflammatory cytokines, the secretion of defence molecules against pathogens and the activation of toll-like receptors (TLRs) and chemosensory cells.[2]

In CRS, mucus clearance is defective owing to the impairment of airway epithelial ciliary function. A decrease in the differentiation of ciliated cells and beating frequency is mediated by Interleukin-13 and interferon-gamma.[8] The increased expression of airway mucin protein, MUC5AC and goblet cell metaplasia with increased mucus production was observed in human CRS sinonasal tissue in response to exposure to cigarette smoke.[9] Several multifunctional proteins are upregulated in the mucus of CRSwNP: cystatin 2, pappalysin-A, periostin, and serpins. The expression of these proteins has been shown to affect barrier integrity and remodelling.[10,11] Epithelial physical barriers are maintained by intercellular junctions, especially tight junctions. Multiple studies demonstrate a reduction in tight junctions and ion permeability in the setting of CRS.[3] Decreased expression of the tight junction proteins occludin-1 and zona occludens 1

TABLE I: THE IMMUNOLOGY OF CHRONIC RHINOSINUSITIS

	INNATE	ADAPTIVE (ALLERGY)					
Mechanism	***Exposure to environmental agents and pathogens***	***Immune system-driven***				***Tissue-driven mechanisms***	***Direct response to chemicals***
	Epithelial barrier	*Antibody-mediated*	*Cell-mediated*			*Epithelial barrier*	
Type of hypersensitivity reaction	NA	Type I	Type IVa T1	Type IVb T2	Type IVc T3	Type V	Type VII
Predominant cells and cytokines	ILC1, ILC2, ILC3, Th1, Th2, Th17, IL-25, IL-33, TSLP, NEU, MON, Mψ, MC, basophils, EOS, NK, DC	B-cells, IgE, Th2, ILC2, mast cells, basophils, IL-4, IL-5, IL-9, IL-13	Th1 Mψ, ILC1, Tc1, NK, IFN-ϒ, TNF-α	Th2 EOS, B cells, mast cells, BAS, ILC2, Tc2, NK-T, IL-4, IL-5, IL-9, IL-13	Th17 NEU, ILC3, Tc17, IL-22, IL-23	Immune modulation (alarmins, TSLP, IL-25, IL-33) Role of neuro-inflammation	
Associated clinical conditions	Primary ciliary dyskinesia, cystic fibrosis	CCAD AFRS	CRSwNP (Asian regions)	CRSwNP (Western regions)		CRSwNP	NSAIDs-exacerbated respiratory disease in rhinitis with or without nasal polyposis

AFRS – allergic fungal rhinosinusitis; CCAD – central compartment atopic disease; EOS – eosinophil; DC – dendritic cells; IFN-y – interferon-gamma; IgE – immunoglobulin E; IL – interleukin; ILC1/2/3 – innate lymphoid cells Type 1/2/3; MC – mast cells; MON – monocyte; Mψ – macrophage; NEU – neutrophil; NK – natural killer cell; NK-T – natural killer T cell; T1/T2/T3 – Type 1/2/3 immune response; Tc1/2/17 – T cytotoxic lymphocyte Type 1/2/17; Th – T helper lymphocytes; TNF-α – tumour necrosis factor-alpha; TSLP – thymic stromal lymphopoietin. (Adapted from [2,4].)

was demonstrated in CRSwNP relative to healthy controls.[12] The airway epithelium secretes defence molecules such as lysozyme, hydrogen peroxide and nitric oxide, which act against pathogens. In CRS, the secretion of oxidases is accelerated, with excessive production of hydrogen peroxide.[13] TLRs are present on the epithelial cell surface and recognise pathogen-associated molecular patterns. Once activated by pathogens, these TLRs trigger the release of cytokines, defence molecules, chemokines and immune cells, which contributes to an inflammatory response.[2] Upregulation of TLR2 and TLR4 occurs in CRSsNP in comparison to CRSwNP and the expression of TLR2 and TLR4 correlates with neutrophil infiltration.[14] When the epithelial barrier integrity in CRS is breached, epithelial cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) are released.[2] These cytokines, also known as alarmins, initiate a cascade of immune activation.[2]

INNATE AND ADAPTIVE IMMUNE RESPONSES

Innate lymphoid cells (ILCs) are activated in response to the epithelial cytokines released and a self-limiting immunological response results. This is characterised by cellular and cytokine responses that target one of three different types of pathogen: Type 1 targeting viruses, Type 2 targeting parasites and Type 3 targeting extracellular bacteria and fungi. Dendritic cells present antigens to T-cells and, in this way, connect the innate and adaptive immune responses. CD4+cells differentiate into five main subsets: Th1, Th2, Th17, follicular helper T-cells and T-regulatory cells.[2] The inflammation in CRS is highly heterogeneous and is characterised by three endotypes: Type 1, Type 2 and Type 3, based on an elevation of canonical T-cell cytokines (Th1, Th2 and Th17 respectively).[3,15,16] Th1 cells release Interferon-ϒ, Tumour necrosis factor-α and Tumour necrosis factor-β. These chemokines stimulate IgG production by B-cells, an increased production of neutrophils and increased local inflammation. Th2 cells release IL-4, IL-5, and IL-13, which contribute to the recruitment of eosinophils and mucus hypersecretion and enhance the production of IgE.[17] The Th17 subpopulation activates neutrophils and monocytes and secretes IL-17A, IL-17F and IL-22.[18] Increased Th2 inflammation with eosinophils is seen in CRSwNP patients in Western regions, whereas increased Th1/Th17 and neutrophils are found in Asian populations and also in patients with nasal polyps.[18,19] Activated B-cells produce specialised immunoglobulins that bind to antigens and neutralise many pathogenic factors.[2] CRSwNP patients have been shown to have higher levels of B-cells than patients with CRSsNP.[2]

NEURO-INFLAMMATION AS A MECHANISM OF AIRWAY INFLAMMATION

Epithelial cells lining the airway collaborate with the nervous system both anatomically and functionally.[2] Activation of solitary chemosensory cells may play a role. It has been shown that autonomic dysfunction symptoms (eg, dry mouth, dry eye, postural dizziness and feeling excessively full after a meal)

TABLE II: KEY DIFFERENCES BETWEEN CRS AND PERSISTENT ALLERGIC RHINITIS		
FEATURE	CHRONIC RHINOSINUSITIS	PERSISTENT ALLERGIC RHINITIS
Aetiology	Multifactorial: microbial infections, epithelial dysfunction, immune dysregulation	IgE-mediated hypersensitivity to allergens
Endotype	Inflammatory subtypes: Type 1, Type 2 and Type 3	Typically Type 2-dominant (Th2-skewed response)
Phenotype	With or without nasal polyps (CRSwNP vs CRSsNP)	Seasonal or perennial based on allergen exposure
Primary symptoms	Nasal obstruction, facial pain/pressure, mucopurulent discharge, hyposmia	Sneezing, nasal itching, rhinorrhoea, conjunctival symptoms
Onset	Often gradual and persistent	Often seasonal or with clear allergen triggers
Duration	≥ 12 weeks (by definition)	Chronic, but may be intermittent < 4 weeks or persistent > 4 weeks
Histopathology	Mucosal thickening, inflammatory cell infiltrates, epithelial disruption CRSwNP – eosinophilic predominant infiltrates, oedematous stroma with pseudocyst formation CRSsNP – neutrophil predominant infiltrate, mucosal fibrosis	Inflammatory cell infiltrates predominantly eosinophilic, goblet cell hyperplasia, no polyp formation
Key immune cells	ILCs, Th1, Th2, Th17, neutrophils, eosinophils	Th2 cells, mast cells, basophils, eosinophils
Common comorbidities	Asthma, aspirin-exacerbated respiratory disease, cystic fibrosis, primary or secondary immune deficiency, ciliary dyskinesia	Asthma, atopic dermatitis, allergic conjunctivitis
Diagnosis	History, physical exam, nasal endoscopy, CT scan	History, physical exam, skin-prick/IgE testing
Treatment approaches	Saline irrigation, corticosteroids, antibiotics, surgery, biologics	Allergen avoidance, antihistamines, corticosteroids, immunotherapy

correlate positively with severity of CRS, especially in CRSwNP patients.[2,20] The immunology of CRS is summarised in Table I.

PATHOPHYSIOLOGICAL OVERLAP BETWEEN CRS AND PERSISTENT ALLERGIC RHINITIS

Allergic rhinitis (AR) is a Type I hypersensitivity reaction (IgE-mediated) driven by allergen-specific IgE and Type 2 cytokines (IL-4, IL-5, IL-13), which leads to eosinophilic inflammation and epithelial dysfunction. Classification according to the Allergic Rhinitis and its impact on Asthma (ARIA) document includes seasonal versus perennial and intermittent versus persistent. [21] The similarity in underlying inflammation between IgE-mediated allergy and CRS, especially in CRSwNP, may lead to the assumption that AR plays a significant role in CRS. However, findings in the literature are contradictory. Wilson et al[22] performed a comprehensive systematic review that evaluated the relationship between IgE-mediated allergy and CRS.[22] Twenty-four articles were included in their review, with almost an equal number of studies supporting or showing no association of allergy with CRS in patients with CRSwNP or CRSsNP.

Although allergens enter the nose via inspiration, this alone cannot introduce allergens into the sinuses. Furthermore, inflammation and polyposis cause obstruction in the meatus, which would make the direct entry of aeroallergens into the sinuses difficult. A putative mechanism is that inhaled allergens are processed by nasal immune cells, which in turn activate T-helper lymphocytes, with downstream inflammation leading to the release of Type 2 inflammatory mediators such as IL-4, IL-5 and IL-13. This in turn activates the production of eosinophils, mast cells and basophils, which precipitates nasal eosinophilia.[22,23] Nasal and paranasal mucosal cells express cell-surface molecules that attract inflammatory mediators and also release inflammatory cytokines, which creates a feedback loop.[21] CRS patients express an abundance of these cell surface-adhesion molecules (such as vascular cell-adhesion molecule-1, or VCAM-1) and chemotactic molecules to recruit inflammatory cells into the sinuses.[22,23,24] This may support a mechanism by which allergens exacerbate CRS. A small number of patients have a condition known as localised AR – these patients test negatively for serum and skin allergy but respond positively to nasal allergen challenge, indicating a local nasal Th2 response. This also suggests evidence for allergy confined to the nasal tissue without systemic involvement.[25] Despite some overlapping pathophysiologic features, conflicting data exist regarding a relationship between allergy and CRSwNP. The key differences between CRS and persistent AR and summarised in Table II.

CLINICAL PHENOTYPES LINKED TO IgE-MEDIATED ALLERGY

More recent literature has shown that two phenotypes of CRSwNP have a stronger link to IgE-mediated allergy: central compartment atopic disease (CCAD) and allergic fungal rhinosinusitis (AFRS).[1,26,27] CCAD is defined by polypoid changes in the central compartment of the nasal cavity, including the middle turbinate, the superior turbinate and the superior nasal septum and was first described in 2014 by White et al.[28] Further reviews by Brunner et al[29] demonstrated a higher association of allergen sensitisation in patients with isolated middle turbinate changes than in those with diffuse polyposis.[29]

Hamizan et al[30] evaluated radiologic findings associated with CCAD and found that a central pattern of mucosal disease had a higher association with allergy.[30] While CCAD is hypothesised to represent a distinct phenotype along the continuum between allergic disease and nasal polyp disease, clarity is needed on whether it is a more diffuse presentation of AR rather than a distinct phenotype of CRS.[31]

AFRS is a subset of polypoid chronic rhinosinusitis that is characterised by the presence of eosinophilic mucin with non-invasive fungal hyphae within the sinuses and a Type I hypersensitivity to fungi.[1,32] Bent and Kuhn[33] included IgE sensitisation as an inclusion criterion in their original description in 1994.[33] AFRS accounts for about 5–10% of CRS cases.[34] Patients presenting with AFRS do so at a younger age than with other types of CRS. Atopy is a pre-defining feature of patients with AFRS and concomitant allergic disease, such as AR and childhood-onset asthma, is common in this group.

DIAGNOSIS AND MANAGEMENT – CLINICAL IMPLICATIONS

The efficacy of allergy therapy in improving the symptoms and quality of life of patients with CRS is limited. In patients with suspected CRS, clinicians should obtain a thorough allergic history and consider allergy testing.[1] In patients with confirmed AR and CRS, an integrated treatment approach is recommended:

1. *Intranasal corticosteroids:* Effective for both allergic inflammation and chronic sinonasal inflammation; it is a first-line therapy.[1]
2. *Allergen avoidance:* Critical for perennial and seasonal disease; reduce exposure to allergic triggers such as dust mites, pet dander and pollen.[1]
3. *Allergen immunotherapy:* There is a paucity of data to support the use of immunotherapy as an adjunctive treatment in CRS patients.[1]
4. *Anti-immunoglobulin E therapy:* Omalizumab is an IgE-targeting therapy which selectively binds free circulating IgE and decreases the expression of IgE receptors on mast cells, basophils and dendritic cells. Previous studies have demonstrated its efficacy in the management of recalcitrant CRSwNP.[35] However, evidence for its efficacy remains mixed and the mechanism of action by which omalizumab is effective in patients with CRSwNP is still being elucidated.
5. *Monoclonal antibody therapy:* Studies collectively support Dupilumab as an effective and well-tolerated option for adult patients with severe CRSwNP. Improvements were noted in nasal polyp size, sinus opacification, nasal obstructive symptoms and the need for surgery.[36] Dupilumab inhibits the signalling of IL-4 and IL-13, which are key drivers of Type 2 inflammation. Targeted biologic therapies such as Dupilumab offer more personalised treatment options for patients with specific endotypes.
6. *Sinus surgery:* For refractory CRS, endoscopic sinus surgery remains a key option to restore drainage and improve access to topical therapies.[1]

CONCLUSION

CRS is a common and burdensome chronic condition that significantly impairs the quality of life of patients. Advancements in the understanding of hypersensitivity and allergic diseases have demonstrated that the pathophysiological mechanisms involved in CRS are heterogenous and complex and involve many overlapping immunological pathways. While it begins with a tissue-driven mechanism involving the disruption of the sinus epithelial barrier which results in a predominantly T-cell-mediated response, the role of antibody-mediated and other factors remains controversial. Whereas IgE-mediated allergy is not the sole cause of CRS, it contributes to the burden of disease in a subset of patients, particularly those with AR. Current effective management requires both allergic and non-allergic mechanisms to be considered, which emphasises a personalised approach based on patient phenotype. Further research is needed to clarify the precise immunological interplay between an underlying inflammation and CRS. Shifting the focus to endotype-driven management and treatment strategies, particularly in the context of emerging biologic therapies targeting Type 2 inflammation, may result in precision or personalised medicine in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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