Management of allergy and sinusitis

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Abstract

Allergic diseases are inflammatory disorders that occur chronically because of immune system activation by environmental factors or allergens. They are classified as type I hypersensitivity reactions mediated by Immunoglobulin E (IgE) antibodies. Atopy refers to the increased sensitivity of IgE antibodies to a specific antigen, with genetic predisposition being one of the risk factors. The clinical relationship between allergy and rhinosinusitis is not clear; however, rhinosinusitis is a result of the inflammation of the sinus mucosa due to the presence of an allergen, and it is either acute or chronic. Rhinosinusitis is, therefore, recognised as an inflammatory disorder of the paranasal sinuses and the nasal cavity. Acute rhinosinusitis (ARS) is usually caused by a viral infection, whereas chronic rhinosinusitis (CRS) is an inflammatory disorder with increased expression of cytokines. Treatments are aimed at reducing mucosal inflammation, thinning and clearing mucus, controlling infection, and treating symptoms such as nasal congestion, rhinorrhoea, sneezing and nasal itching. The goal of this article is to outline the current management approach for rhinosinusitis and review new treatment options and therapeutic techniques.

Keywords: allergy, sinusitis, inflammatory disorders

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Introduction

Allergic diseases are a group of chronic, systemic, inflammatory disorders that occur because of the immune system's excessive activation by certain environmental factors, also known as allergens. Allergens are grouped into chemical allergens, such as dyes; food allergens, such as nuts; and aeroallergens, such as pollen.[1,2,3] This type I hypersensitivity reaction is specifically mediated by the humoral immune system in which an allergen or antigen binds to allergen-specific immunoglobulin E (IgE) on the surface of mast cells. This binding results in the release of inflammatory mediators such as histamine.[2-6] Allergic diseases are known to be complex because, additionally, they can occur because of genetic predisposition, in which IgE antibodies have increased sensitivity to a specific antigen and are produced in response to minor exposure to environmental chemicals that would not be a trigger under normal circumstances. This is referred to as atopy.[1,2] During pregnancy or early childhood, environmental factors can alter the physiologic, immune, structural, and behavioural development and, therefore, alter the response patterns and create susceptibility to future diseases. Other than genetic predisposition, atopy risk factors include decreased exposure to infections and endotoxins, postnatal antibiotic use, air pollutants, exposure to allergens, gestational use of antibiotics and maternal stress.[3,4] Complex interactions between genetic and environmental factors result in different allergic diseases, such as allergic rhinitis, allergic asthma, atopic dermatitis, food allergy, and eczema, which also exist. Other common allergic conditions globally include rhinosinusitis, allergic conjunctivitis, and allergic oesophagitis. The prevalence of allergic diseases is on the rise, affecting 30% to 40% of the world's population. According to the World Health Organization (WHO), allergic diseases are among the top three disorders to be prevented and controlled in the 21st century.[4,7]

Pathophysiology of allergy and symptoms

The early and late phases of an allergic response

The body's response to an allergen occurs in two phases, i.e. the early and late phases. The presence of an allergen attracts antigen-presenting cells (APCs), such as dendritic cells found on the mucosal surface. The dendritic cells process and present peptides from allergens on the major histocompatibility complex (MHC) class II molecule, forming a complex. This complex forms a ligand for Naïve $CD4^+$ T-cell receptors and, once attached, differentiates the Naïve $CD4^+$ T-cells to activated allergen-specific Th2-cell. Th2-cells are responsible for the secretion of several cytokines, such as IL-4 and IL-5, which stimulate B cells to produce specific IgE antibodies and stimulate the proliferation of eosinophils, mast cells and neutrophils. The resultant antigen-specific IgE binds to high-affinity Fc receptors for IgE on mast cells or basophils.[8,9] The cross-linking of these receptors on mast cells causes the release of inflammatory mediators such as histamine, prostaglandins, and leukotrienes, which cause vascular leakage, bronchoconstriction, inflammation and intestinal hypermotility. These inflammatory mediators induce mucosal oedema and watery rhinorrhoea by causing blood vessels to leak.[9,10] Histamine activates H_1-receptors on sensory nerve endings, causing sneezing and pruritis. Histamine further exacerbates symptoms in what is called reflex secretory response by interacting with H_1 and H_2 receptors on mucosal blood vessels, leading to vascular engorgement (nasal congestion) and plasma leakage.[9] The early phase presents the rapid onset of acute symptoms such as itching, sneezing and rhinorrhoea, which develop within less than 20–30 min after allergic exposure.[11] The mediators further play a role in the late reaction, which occurs 4–6 hours after allergen exposure and subsides slowly. In this phase, eosinophil chemotaxis triggered by cytokines occurs, where several inflammatory cells, including eosinophils, migrate

to the nasal mucosa, breaking up and remodelling normal nasal tissue, resulting in nasal mucosal inflammation and obstruction. The schematic representation of the pathophysiology of allergic rhinitis is illustrated in Figure 1.[8-10]

Allergy and sinusitis

Sinusitis or rhinosinusitis is defined as a symptomatic inflammatory condition involving the paranasal sinuses and the nasal cavity.[12,13] The condition is classified as acute, sub-acute and chronic based on the duration. Acute rhinosinusitis (ARS) lasts up to four weeks, sub-acute rhinosinusitis lasts between 4–12 weeks and chronic rhinosinusitis (CRS) for more than 12 weeks. ARS is mainly due to bacterial, fungal, or viral infections, as well as allergens or exposure to inhaled irritants. It presents with common symptoms such as purulent nasal drainage accompanied by nasal obstruction and/or facial pressure pain. Other symptoms associated with ARS, which are not required for diagnosis, include malaise, reduced sense of smell, maxillary pain, and increased ear pressure.[4,12] CRS symptoms overlap with other conditions, especially allergic conditions, such as allergic rhinitis, and therefore, differential diagnosis is essential. Although extensively studied, the clinical relationship between allergy and rhinosinusitis is unclear.[14,15] In some studies, the cause-and-effect was proposed as the relationship between allergy and chronic sinusitis; however, in one study, the mention of systemic involvement in allergic reactions rather than local involvement provides insight into the mechanism underlying allergy and rhinosinusitis. Allergens can mostly not cross into the paranasal sinuses; however, once inhaled, the T-cell immune response is initiated.[16,15,17] The resultant inflammation of the sinus mucosa due to the presence of an allergen is also referred to as allergic rhinosinusitis, which can be either acute or chronic. The inability of the nose to eliminate the allergen results in an environment of chronic inflammation.[4] It has become accepted that chronic inflammatory processes play a role in the occurrence and development of chronic sinusitis, and unlike ARS, the aetiology of CRS displays more complex characteristics of inflammation.[4,13,15] Notably, patients who have CRS present with persistently inflamed mucous membranes, irrespective of the actual presence of allergens in the nasal cavity.[16] CRS is characterised by the type of inflammation, Type 2 (IL-5 and IL-13), Type 1 (IFN-γ) and Type 3 (IL-17A) and is further subdivided into three types, namely CRS without nasal polyps (CRSsNP), CRS with nasal polyps (CRSwNP) and allergic fungal rhinosinusitis.[18] The contribution of type 1 and type 3 inflammation to CRS is not understood. Majority of CRS especially CRSwNP exhibit type 2 inflammation.[18,19,20] There are other causes that play a role in the pathogenesis of rhinosinusitis, such as epithelial tissue hypersensitivity, disruptions of innate immunity and, the presence of bacterial colonisation and biofilm, and genetic and environmental factors. Inflammation is a common denominator for these various causes. Therefore, allergies such as allergic rhinitis may produce rhinosinusitis, supported by the fact that 25–58% of people with rhinosinusitis have some form of inhaled allergen sensitisation. Allergy may also exacerbate CRS by adding to the existing inflammation. This theory is encouraged

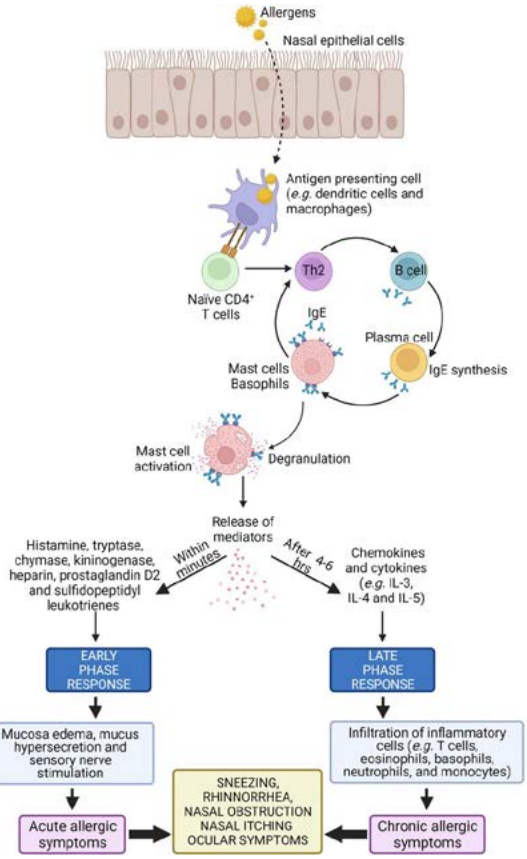

Figure 1: Schematic presentation of the pathophysiology of AR.[9]

by the fact that in CRS, the cell surface adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and other chemotactic molecules are expressed in abundance and have been assumed to form a part of the mechanism by which AR mediates CRS. In a study involving mice, hyper-responsiveness to histamine was demonstrated in a mice model of acute bacterial sinusitis where sinusitis was enhanced during exposure to aeroallergens.[20] Staphylococcus species found in the nose and paranasal sinuses can create a biofilm that becomes a source of superantigen and inflammation regardless of their inactive biofilm state. The superantigens further exacerbate the inflammatory response by triggering IL-4, IL-13 and TH2 cytokines that lead to IgE in the sinus tissues.[16,20] The resultant inflammation further prevents the clearance of bacteria from the sinus cavity, which may lead to the development of secondary bacterial sinusitis.[4,16]

Management of rhinosinusitis

Intranasal saline irrigation

Hypertonic intranasal saline irrigation is recommended for the supportive treatment of CRS due to its minor adverse effects, although irritation of nasal mucosa and burning sensation may occur.[12,21] The hypertonic solution, compared to the isotonic solution, proved to be superior in thinning and clearing mucus. Saline irrigation is expected to have anti-inflammatory effects and plays a role in removing inflammatory mediators such as histamine and prostaglandins. Moreover, saline irrigation directly

cleans the mucus to prevent bacterial growth.[13,21] It provides symptomatic relief from nasal congestion, rhinorrhoea, cough, and headache and prevents the condition from worsening.[12,21,22] Saline irrigations are affordable and can be administered at home.[21] In various guidelines, nasal irrigation is encouraged as a first-line treatment to avoid the overuse of antibiotics for CRS. Additionally, nasal irrigation promotes wound recovery in the nasal cavity and sinuses post-endoscopic sinus surgery (ESS), further preventing the use of unnecessary drugs post-surgery. The limitation to saline irrigation is the indirect flow as opposed to directly penetrating the sinuses, considering the complex structure of the sinuses with its various connections.[13]

Corticosteroid therapy

Intranasal (topical) corticosteroids are beneficial in both ARS and CRS.[12,23,24] They have proven efficacy in the treatment of allergic rhinitis as well as all forms of CRS, especially CRSwNP.[18,19] Corticosteroids suppress type 2 inflammation, which is typical of CRS. The suppression of type 2 inflammation results in the suppression of eosinophils and Th2-cells. The mechanism of action of corticosteroids involves the attenuation of the expression and release of pro-inflammatory cytokines from airway epithelial cells, therefore reducing inflammatory mediators and immunoreactive cells. Topical corticosteroid nasal sprays are recommended to prevent the recurrence of small to medium nasal polyps, although not always effective. In most cases, they are beneficial for the rhinitis symptoms.[19,25] The limitation to intranasal corticosteroids is the inconsistent nasal distribution in the presence of severe nasal mucosal oedema or large nasal polyps.[26] The inconsistent distribution is also because most formulations are low-volume devices (i.e. spray bottles), which do not provide an effective spray to penetrate sinuses optimally, especially ethmoids (Figure 2).[27] The solution to this could be the use of large-volume devices such as nasal irrigation or the change in position of the low-volume devices to maximise penetration. Although large-volume devices improve sinusitis nasal symptoms, the long-term safety has not been evaluated further.[18,26] Examples of intranasal corticosteroids include beclomethasone, budesonide, fluticasone, mometasone, triamcinolone and ciclesonide. The newer agents, i.e. mometasone, fluticasone and ciclesonide, have minimal systemic effects. Corticosteroids are effective at recommended doses without adrenal suppressive effects.[12,18,25] They are intended for short-term use to avoid adverse effects associated with long-term use, such as atrophy of the nasal mucosa.[4,25] The most common local side effects experienced with intranasal corticosteroids include nasal irritation or burning, stinging, dryness and crusting, and epistaxis. Oral or systemic corticosteroids can be used, as a brief course of 10-15 days, to shrink nasal polyps and may also be used in allergic fungal sinusitis. They are considered in cases of severe CRS when rapid symptomatic relief is needed (i.e. CRS flare-ups or in the postoperative period after sinus surgery).[26] In such instances, a tapered regimen of oral steroids is preferred. Oral corticosteroids include hydrocortisone, cortisone acetate, prednisone, prednisolone, and methylprednisolone.[28,29] Although

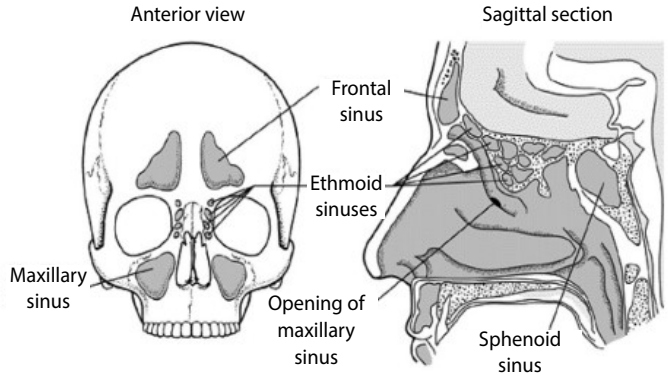

Figure 2: Anatomy of the paranasal sinuses.[27]

the combination of long-term decongestants with intranasal corticosteroids for CRS requires additional investigation, it is believed that topical decongestants may enhance the delivery of intranasal corticosteroids even in the presence of mucosal oedema.[30]

Decongestants (local and systemic)

Decongestants in rhinosinusitis are used for the relief of nasal congestion caused by mucosal oedema and local vasodilation, but there is little evidence in their role with regards to the quicker resolution of rhinosinusitis. Belonging to the drug class α-adrenergic agonist, decongestants relieve nasal congestion by inducing the release of norepinephrine from sympathetic nerves leading to nasal vasoconstriction. Topical decongestants improve acute symptoms in patients with rhinosinusitis but may reduce mucosal blood flow, which may increase inflammation and increase ciliary loss. The most used topical decongestants include xylometazoline, phenylephrine and oxymetazoline. Topical decongestants should not be used for longer than 3–5 days to avoid undesirable effects such as rhinitis medicamentosa.[4,25,30] Systemic decongestants include direct-acting (phenylephrine) and indirect-acting (pseudoephedrine). They are often combined with antihistamines, especially older generation H1-antihistamine, in preparations which may cause drowsiness and a lack of motor coordination. Their general non-selectivity results in other α-adrenoceptor stimulating effects not limited to the nasal cavity, such as hypertension, insomnia, and appetite suppression.[4,12]

Antihistamines

Although not indicated for use in bacterial ARS, antihistamines are first-line therapy for ARS with underlying allergic rhinitis.[12,25,31,32] Antihistamines are divided into first-generation and second-generation antihistamines and exert their action by competitive inhibition of the histamine receptors on airway mucosal cells. Second-generation antihistamines include cetirizine and levocetirizine, loratadine, desloratadine, ebastine, fexofenadine and mizolastine and have a higher affinity for histamine receptors with less sedating anticholinergic effects as compared to the first-generation antihistamines that cross the blood-brain barrier. First-generation antihistamines include promethazine, chlorpheniramine, dexchlorpheniramine and cyclizine.[4] They

are the most effective in atopic patients with symptoms such as rhinorrhoea, sneezing and nasal itching, which shows an improvement in sneezing after 14 days and have modest effects on nasal congestion, with improvement showing after 28 days. The use of antihistamines over a long time is more beneficial and effective than on-demand therapy.[12,31,33] All H1 antihistamines have anti-inflammatory properties due to their inhibition of the synthesis of the histamine-activated NF-κB, a transcription factor involved in the synthesis of pro-inflammatory cytokines and adhesion molecules. The effect is evident when taken on a regular daily dosing schedule rather than on an as-needed basis.[12] However, they can cause excessive drying, which can cause thickening of mucus and, therefore, impair mucus clearance. Therefore, there is no sufficient evidence to support the use of oral or intranasal antihistamines in both ARS and CRS.[25,26,34]

The leukotriene receptor antagonists

Examples of leukotriene receptor antagonists include zafirlukast and montelukast.[4] Montelukast is the only orally active leukotriene receptor antagonist that is approved for the treatment of allergic rhinitis.[12,25] It acts by binding to the leukotriene-1 receptor with high affinity and selectivity, thereby inhibiting the physiologic actions of leukotrienes in the upper respiratory system. It also reduces the number of eosinophils and, therefore, acts on a systemic level to reduce allergic inflammation. The evidence to support leukotriene receptor antagonists in the treatment of CRSwNS is moderate, especially when combined with topical or oral corticosteroids.[25,35] Montelukast is also available as a sprinkle and a chewable tablet for use in paediatrics[4] but is not currently registered as an over-the-counter drug for allergic rhinitis and rhinosinusitis because of the neuropsychiatric adverse effects associated with the drug such as depression, aggression, insomnia, irritability, and nightmares that were reported post-marketing.[36]

Immunotherapy/Monoclonal Biologic Therapies

This includes agents such as omalizumab (anti-IgE), reslizumab (anti-IL-5), mepolizumab (anti-IL-5) and dupilumab (anti-IL-4Rα).[37] A summary of the biologic medications is shown in Table I. Immunotherapy is only indicated, as an adjunct, in patients with moderate to severe refractory allergic rhinitis and CRS.[18,26] In South Africa, the only monoclonal IgE antibody registered is the subcutaneous omalizumab. Omalizumab works by binding to high levels of circulating, allergy-associated IgE antibodies and removes them from the circulation, thereby inhibiting the antibodies' ability to cause mast cell degranulation and subsequent allergic reactions.[12] Based on data from various studies, one study being a meta-analysis comparing IgE therapy to placebo in subjects with CRSwNP, there is a potential clinical efficacy of omalizumab for CRSwNP, favouring those with comorbid asthma.[18,38]

Antibiotics

Antibacterial agents in CRS are used to treat acute bacterial exacerbations where purulence draining from the sinuses is identified and are often prescribed in combination with topical nasal steroids and other adjuvant therapies.[18,25] Experts say that antibiotics used in CRS should have a broad spectrum. Antibiotics used for acute and CRS include amoxicillin-clavulanic acid, erythromycin, clindamycin, levofloxacin and ciprofloxacin or moxifloxacin, cefuroxime, doxycycline, co-trimoxazole for a duration of 10–14 days. Short-term antibiotic therapy (up to seven days) has a similar efficacy and outcome as long-term therapy (≥ 2 days longer than short-term) and has the benefits of less antibiotic-associated side effects.[12,25,39] However, there is inconclusive evidence for the optimal duration of therapy, most clinicians can prescribe from seven days to four weeks.[26] Evidence based on a 2016 Cochrane review of a limited number of placebo-controlled trials shows that there could be benefits with long-term antibiotic therapy especially for type 3 inflammation.[13,18] The general approach is to continue antibiotics until the patient is asymptomatic and has no mucopurulent discharge.[18] Amoxicillin is considered the first-line treatment in acute and CRS because of its favourable side effect profile. Monotherapy is sufficient in low-risk patients, but the combination with clavulanic acid is recommended in children, the elderly and patients who are more likely to have bacterial resistance, e.g. patients who were recently treated with antibiotics. Macrolides or fluoroquinolones are preferred in penicillin-allergic patients.[18,25] According to a survey, 94% of otolaryngologists prescribed oral antibiotics for CRS.[25] The limitation to antibacterial prescribing for acute and CRS, even with demonstrated efficacy, is the rise in resistant organisms. Bacteria cultured from purulence in CRS demonstrated resistance as compared with ARS. Therefore, according to antimicrobial stewardship the use of antibiotics should be only if necessary.[12,13]

Conclusion

Rhinosinusitis remains a prevalent disease and has a significant

Table I: Biologic Medications Approved or Being Evaluated for CRSwNP.[16]

	Dupilumab	Omalizumab	Mepolizumab	Benralizumab
Pharmacology	Fully human monoclonal anti-IL-4 alpha subunit antibody	Recombinant humanised monoclonal anti-IgE antibody	Recombinant humanised monoclonal anti-IL-5 antibody	Recombinant humanised monoclonal anti-IL-5 receptor alpha subunit antibody
Indication	Moderate to severe asthma with eosinophilic phenotype or with oral corticosteroid dependent asthma, atopic dermatitis, CRSwNP	Moderate to severe asthma with positive allergy testing, chronic urticaria	Severe asthma with eosinophilic phenotype, eosinophilic granulomatosis with polyangiitis	Severe asthma with eosinophilic phenotype

impact on overall quality of life. In this article, difference between acute and CRS were summarised and the fact that allergic rhinitis and rhinosinusitis are two distinct conditions that usually overlap and can coexist in a patient were highlighted. The management was discussed; the different available drugs and their mechanisms to improve overall disease prognosis. The current available treatments aim to reduce inflammation, which is a main cause of rhinosinusitis. Advancements in therapy, such an immunological therapy have significantly improved the management of rhinosinusitis patients and help reduce morbidity. Further evidence-based research must be done to encourage some of the recommended treatment options.

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