

**CHRONIC RHINOSINUSITIS (CRS): CURRENT CONCEPTS IN ETIOLOGY AND
PATHOPHYSIOLOGY WITH NOVEL THERAPEUTIC APPROACHES*****¹Arya Chandran, ¹Lekshmy Satheesh, ²Angela A. Thomas, ²Dr. Aneeta Toms**¹Sixth Year Pharm D Intern, The Dale View College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala.²Associate Professor, Department of Pharmacy Practice, The Dale View College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala.***Corresponding Author: Arya Chandran**Sixth Year Pharm D Intern, The Dale View College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala. DOI: <https://doi.org/10.5281/zenodo.23033085>**How to cite this Article:** *Arya Chandran, Lekshmy Satheesh, Angela A. Thomas, Dr. Aneeta Toms (2026). Chronic Rhinosinusitis (CrS): Current Concepts In Etiology And Pathophysiology With Novel Therapeutic Approaches. World Journal of Pharmaceutical and Medical Research, 12(10), 36-47.

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INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease of the paranasal sinuses, which commonly results in chronic sinonasal symptoms. In the United States, 1% to 5% of the population has chronic rhinosinusitis. CRS is defined as 2 or more of 4 cardinal signs and symptoms (i.e., facial pain/pressure, hyposmia/anosmia, nasal discharge [anterior and/or posterior], nasal obstruction) irrespective of previous history of acute rhinosinusitis for a duration exceeding 12 consecutive weeks.^[1]

ETIOLOGY

CRS does not have a single cause; rather, it results from a complex interaction between host-related factors and environmental factors, leading to persistent sinonasal mucosal inflammation.^[2,3]

Fungal hypothesis and super antigen hypothesis

Two main hypotheses have sought to explain the etiology of chronic rhinosinusitis (CRS) as a reaction to frequent intranasal microorganisms: the *Alternaria* 'fungal hypothesis' and the *Staphylococcus aureus* (S. aureus) 'superantigen hypothesis.' The recent review highlighted the advantages of these hypotheses. In summary, the 'fungal hypothesis' posits that an exaggerated host response to the widespread airborne fungus *Alternaria* serves as the primary pathogenic trigger for all forms of CRS, whether polypoid or nonpolypoid, with variability only in intensity. It indicates that *Alternaria* not only triggers an immune response through T cells but also acts as a target for eosinophils, leading to degranulation and damage to tissues. The main evidence supporting the fungal hypothesis is the increased hyperreactivity of peripheral blood mononuclear cells (PBMCs) from patients with CRS when stimulated with high doses of *Alternaria* antigen. This enhanced response likely indicates an immunologic sensitization to *Alternaria*, implying its significant role in initiating the inflammatory response associated with CRS. However, it is worth noting that the

majority of the patients (78%) involved in the study also had asthma, which may account for the observed increases in PBMC responsiveness. Additionally, fungi, especially *Alternaria*, possess intrinsic proteases that can nonspecifically activate protease-activated receptors (PARs) located on the cell surface. As a result, the exposure of activated PBMCs to elevated levels of proteases might explain the increased in-vitro reactions through non-antigen-specific mechanisms, rather than a targeted response to *Alternaria* antigens. The nonspecific effects of a protease might not be negligible, considering that epithelial-based PARs are known to be upregulated in chronic rhinosinusitis (CRS). In conclusion, while significant amounts of *Alternaria* or other fungi may have direct immunostimulatory effects, we still do not have compelling in-vitro or in-vivo proof that fungal antigens are the focus of the mucosal T cells or B cells in CRS.^[5,6,7,8,9,10,11,12,13,14,15,16,17,18]

Immune barrier hypothesis

The fungal and superantigen hypotheses, although often seen as opposing, both highlight that unidentified host factors influence susceptibility to disease from common environmental agents. This idea of a dysfunctional host-environment interaction underpins current research into chronic rhinosinusitis (CRS). The sinonasal epithelium acts as the interface with inhaled irritants, microbes, and pathogens, using mechanisms like mucociliary clearance, physical barriers, and immune responses to protect the

host. Failure of mucosal defenses leads to chronic inflammation and CRS symptoms.^[2,20,21,22,23,24]

The immune barrier hypothesis centers on host defects as key to CRS etiology.

Research increasingly focuses on host susceptibility over environmental factors.^[2,20,21,22,23,24]

Similar trends are observed in chronic inflammatory diseases affecting epithelial surfaces (e.g., atopic dermatitis, psoriasis, asthma, IBD).^[2,20,21,22,23,24]

CRS susceptibility is likely specific to the airway epithelium, not systemic immune issues.^[2,20,21,22,23,24]

Genetic studies in related diseases show polymorphisms affecting epithelial proteins, supporting the epithelium's role.^[2,20,21,22,23,24]

3. Physical barrier defects in chronic rhinosinusitis

A growing body of research indicates that the disruption of the mechanical aspect of epithelial barrier function can be crucial in allowing foreign proteins to trigger an immune response in a number of chronic mucosal inflammatory disorders. Significantly lower tight junction proteins and higher ion permeability in comparison to normal controls are indicators of barrier disruption in CRS. More recently, research conducted in our lab showed that CRS patients had considerably lower levels of SPINK5, which codes for the protein LEKT1, a protease inhibitor involved in preserving epithelial barrier function. Netherton syndrome, a rare autosomal recessive disorder characterised by dry skin, weak hair, and severe atopy, has been linked to genetic abnormalities in SPINK5. Increased sensitivity to endogenous and exogenous protease activity may arise from lower levels of protease inhibitors such as LEKT1 in CRS epithelium. It's interesting to note that dust mites, fungus, and bacteria all have high intrinsic protease activity. This could make the mechanical barrier more susceptible to protease attack in the presence of insufficient endogenous protease inhibitors like LEKT1. Increased mucosal penetration of foreign proteins and consequent amplification of the inflammatory response through stimulation or antigenic stimulation may result from the breakdown of the mechanical barrier.^[23,24,25]

4. Innate immune dysfunction in chronic rhinosinusitis

The innate and acquired components of the human immune response overlap and are both vital to host defence. The first line of defence against pathogens is provided by the innate immune system, which is made up of cells and the processes that work with them. These pathways are genetically programmed and have limited molecular structural specificity. It has been demonstrated that the sinonasal mucosa expresses a wide range of antimicrobial compounds in addition to the physical barrier and pathogen clearing functions of the mucociliary clearance system. Previous research on CRS generally did not show consistent changes in the expression of these antimicrobial compounds; certain molecules were found to have higher levels, while others were reported to have lower levels. Sinonasal epithelial

cells carry pattern-recognition receptors (PRRs), which identify pathogen-associated molecular patterns (PAMPs), in addition to secretory antimicrobial proteins. Toll-like receptors (TLRs) are prominent PRRs that, when activated, cause a pro-inflammatory response by activating nuclear transcription factors such as IRF3, AP-1, and NF- κ B. Since TLR2, TLR3, TLR4, and TLR9 are expressed in the airway, it is believed that they are crucial in mediating host inflammation, with possible disruptions leading to the onset of CRS. The quantitative rise in TLR2 mRNA observed in both CRSsNP and cystic fibrosis polyps lends credence to this theory. The cytokine IL-22, which is released by Th17 and Th1 cells and stimulates epithelial cells through the IL-22 receptors (IL22R), is a significant inducer of innate immune responses. When compared to controls, nasal polyposis in CRSwNP was found to have considerably lower levels of IL22R1, indicating a reduced IL-22 response in CRSwNP.^[26,27]

5. Activation of adaptive immunity through epithelial-mediated mechanisms in chronic rhinosinusitis

Through a variety of methods, the epithelium also plays a significant role as a mediator in attracting and stimulating the adaptive immune system. First, through cell surface chemicals that can directly interact with and control T cell activation, epithelial cells mediate communication between the environment and the adaptive immune system. Second, B cells, dendritic cells, and T cells are activated by strong soluble cytokines produced by epithelial cells, such as BAFF, TSLP, and interferon (IFN)- γ . Third, chemokines produced by epithelial cells draw in and facilitate the movement of adaptive immune system cells. Finally, as was previously mentioned, epithelial cells have the ability to release and react directly to cytokines like IL-22 that are released by the cellular immune system. Therefore, nasal epithelial cells seem to play a key role in both immediately reacting to external stimuli and facilitating communication with other cell types implicated in mucosal immunity. The future development of CRS may be significantly influenced by dysfunctional or dysregulated interactions between the epithelium and various other cell types. Dendritic cells, which are abundant in nasal epithelial tissue and serve as antigen-presenting cells by collecting and processing peptides from the environment to deliver to T and B cells, are important targets for nasal epithelial crosstalk. Common viruses like rhinovirus can substantially produce TSLP, a crucial airway epithelial protein. The helper cell response is polarised in a Th2 direction by dendritic cells when TSLP levels are high. Additionally, new research indicates that TSLP synthesis may rise in the absence of protease inhibitors such as LEKT1. This supports the previously reported theory that lower LEKT1 levels in CRS may intensify epithelial cells' TSLP response to rhinovirus, explaining the elevated Th2 response seen in some types of CRS. This intriguing theory may help connect protease activity at the epithelial surface with the production of a Th2 response, even if increased TSLP

levels in CRSwNP have not been shown at the protein level.^[26,27,28,29,30,31,32,33]

CLINICAL MANIFESTATIONS

1. Nasal obstruction / nasal congestion Persistent sensation of blocked nose due to mucosal edema, polyps, or secretions.^[34,35,36,37]
2. Nasal discharge (anterior or posterior nasal drip) Thick mucopurulent or watery discharge; post-nasal drip commonly causes throat clearing.^[34,35,36,37]
3. Facial pain, pressure, or fullness Typically over maxillary, frontal, or ethmoid sinuses; less prominent than in acute sinusitis.^[34,35,36,37]
4. Reduction or loss of smell (hyposmia/anosmia) Especially common in CRS with nasal polyps due to olfactory cleft inflammation.^[34,35,36,37]
5. Headache Dull, non-pulsatile; often overlaps with facial pressure.^[34,35,36,37]
6. Chronic cough More common in children; caused by post-nasal drip.^[34,35,36,37]
7. Fatigue and malaise Reflect chronic inflammation and sleep disturbance.^[34,35,36,37]
8. Halitosis Due to retained infected secretions.^[34,35,36,37]
9. Dental pain (upper teeth) Secondary to maxillary sinus involvement.^[34,35,36,37]
10. Ear fullness or pressure Due to Eustachian tube dysfunction.^[34,35,36,37]

CLASSIFICATION OF CHRONIC RHINOSINUSITIS

The long-term inflammatory disease known as chronic rhinosinusitis (CRS) has a significant financial and social impact on the world. Its prevalence is estimated to be 10–28% based just on self-reported symptoms, and roughly 4–9% when imaging or endoscopy is used. Based on the visual analogue scale for rhinosinusitis, real-world statistics indicate that about half of CRS patients have uncontrolled disease.⁹ Due to the fact that these individuals frequently need repeated sinus operations, medication, and long-term follow-up, this subgroup has a substantial disease burden. The presence or absence of nasal polyps has historically been used to categorise CRS. It is clear that this visual trait-based classification is likely an unduly simplified depiction of a heterogeneous illness with a range of clinical manifestations and severity. The most recent edition of the European Position Paper on Rhinosinusitis and Nasal Polyps is devoted to a thorough analysis of the most recent rhinosinusitis research. This edition included a number of updates. The suggestion of a new classification system for CRS that is no longer based on the polyp phenotype is a significant aspect of this review. Depending on the anatomic distribution of the disease, CRS is now first classified as either primary or secondary CRS and then divided into localised and diffuse disease. In primary diffuse CRS, this is further classified as either a type 2 or non-type 2 endotype.^[35,38,39,40,41,42,43]

CRS ENDOTYPES

TYPE 2

CRS is currently classified as either type 2 or non-type 2 endotypes (Figure 2). Because type 2 inflammation is linked to difficult-to-treat CRS, it has drawn more attention than the other group, indicating an unmet need for efficient treatment solutions. The T helper 2 (Th2) cell and innate lymphoid cell 2 (ILC2), which generate the cytokines IL-4, IL-5, and IL-13, are the primary effectors in this endotype. Goblet cell hyperplasia and tissue remodelling are caused by IL-13's additional interactions with Yes-associated protein in the Hippo pathway. Type 2 inflammation is similarly characterised by elevated IgE and eosinophils. Eosinophils produce a variety of lipid mediators, including as prostaglandins, cysteinyl leukotrienes, and mediators generated from 15-lipoxygenase (15-LOX). In type 2 CRS, this synthesis is compromised, leading to a pro-inflammatory condition akin to severe asthma. Allergy and parasite infections are traditionally linked to the type 2 immune response. This endotype is typically linked to loss of smell in clinical settings. This could be caused by reduced olfactory neurone regeneration as well as mast cell and eosinophil infiltration into the olfactory mucosa. Additionally, adult early-onset or late-onset asthma, which frequently exhibits type 2 inflammation, is more frequently linked to type 2 CRSwNP.^[43,44,45,46,47,48,49]

NON-TYPE 2

Both type 1 and type 3 inflammation are included in the non-type 2 endotype. Typically, intracellular bacteria and viruses trigger the type 1 immune response. Interestingly, viruses are linked to lower objective endoscopic and CT sinus scores in CRS without nasal polyposis (CRSsNP), but not in CRSwNP. ILC1 and T helper 1 (Th1) cells mediate type 1 inflammation. Mononuclear phagocytes are activated by Th1 cells and generate interferon gamma (IFN- γ), a characteristic indicator of type 1 inflammation. IFN- γ increases neutrophil activity and causes nasal epithelial cells to undergo apoptosis. In polyp tissue, activated neutrophils with elevated CD16 and decreased CD62L expression are upregulated and in charge of phagocytosis and reactive oxygen species release. Hypoxia-induced factor-1-alpha (HIF-1 α) in non-eosinophilic nasal polyps causes macrophages to produce inflammation, which exacerbates airway inflammation. Extracellular bacteria and fungi cause type 3 inflammation by stimulating the production of osteopontin by epithelial cells. The cytokines IL-17, IL-22, and IL-23 are produced when osteopontin activates dendritic cells to cause Th17 cell differentiation. Purulent nasal discharge is clinically linked to this subtype of inflammation.^[25,51,51,52,53,54,54,55,56,57,58,59]

CHALLENGES WITH ENDOTYPING

Despite the aforementioned endotypes, patients don't always fit neatly within the designated groups. Classifying CRS patients into either group is challenging because over 25% of them have mixed endotypes. Since molecular pathways can be connected in a variety of

ways, overlapping endotypes are scarcely surprising. For instance, strong neutrophilic reactions can be induced by Charcot-Leyden crystals in eosinophilic mucin. Both eosinophilic and non-eosinophilic CRSwNP had elevated hippo pathway components. Cold-inducible RNA-binding protein is released by nasal epithelial cells and macrophages, causing tissue remodelling and oedema in both eosinophilic and non-eosinophilic polyps. High concentrations of neutrophils and non-type 2 cytokines can also be found in eosinophilic nasal polyps. Compared to patients with a single major endotype, those with mixed-pattern inflammation typically have higher symptom levels, a higher cytokine burden, and mucin hypersecretion. Choosing the best anatomic location for endotyping is another difficulty because it is yet unclear. There is some evidence that the sinonasal cavity does not have a uniform distribution of inflammatory cytokines, and that cytokine levels may differ depending on where in the nose one is. The ethmoid sinuses had significantly higher amounts of IL-17A and Charcot-Leyden crystal galectin than the uncinate and inferior turbinate in a study on CRSsNP. IL-5 was elevated in all paranasal sinuses but not the middle turbinate, according to a different investigation on severe CRSwNP. Confounders must also be taken into account. It is generally known that the CRS endotypes vary geographically. While the main endo-type tends to vary among Asian cultures, type 2 inflammation is more common in Caucasian populations. The kind and intensity of inflammation can also be influenced by age. Compared to their younger counterparts, CRS patients 60 years of age and older seem to show type 1 inflammation more frequently. Additionally, they display a subpopulation of polymorphonuclear neutrophils that produce less reactive oxygen species and have a lower phagocytic index, which may lessen the inflammatory response. These results imply that the development of a certain inflammatory endotype may be influenced by a variety of [51,54,54,55,56,57,58,59,60,61,62,63] intrinsic and extrinsic variables.

PATHOPHYSIOLOGY OF CHRONIC RHINOSINUSITIS

1. ACQUIRED IMMUNITY, T CELL SIGNATURES

The subsets of T cells and B cells that make up the acquired immune system have distinct capacities to combat infections and control inflammation. Certain lymphocyte compositions define CRSsNP and CRSwNP; in particular, T helper cell signatures do significantly influence the kind of mucosal inflammation in terms of neutrophilic vs. eosinophilic predominance. Th1, Th2, and Th17 cells are the most common Th cell signatures in CRS that we can currently identify. Pilot experiments in upper airway mucosal tissue revealed that Th1 cells that produced interferon-gamma were common for CRSsNP, while Th2 cells that produced interleukin-5 were usually seen in CRSwNP. Later research conducted with Chinese colleagues showed that the picture is considerably more complicated, with Th1, Th2, and

Th17 cells coexisting in the mucosa of the airways, and that the proportional distribution of those cells would vary significantly between continents. In contrast to China, where polyps mostly show a Th17 cell profile, over 80% of polyps in Caucasians express a Th2 profile. However, the majority of Caucasian nasal polyps in patients with cystic fibrosis also exhibit a distinctive Th17 signature. Recent research revealed that Th cell signatures may vary from person to person, necessitating a much more focused examination of T cell clusters controlling inflammation in patient subgroups that may be linked to significantly different co-morbidity profiles. The staphylococcal superantigen SEB is one of the triggers for IL-21 expression, and IL-21 and IL-21-producing T follicular helper (Tfh)-like cells have recently been found to be an increased population in nasal polyposis. The authors hypothesise that via promoting local immunoglobulin production and germinal centre formation, T-follicular helper cells and their byproduct, IL-21, play a significant role in the pathophysiology of nasal polyposis. In addition to an increase in T cells, CRSwNP has markedly elevated B and plasma cell counts, indicating a highly stimulated local immunoglobulin synthesis. This up-regulation may be partially explained by the overproduction of B cell-activating factor of the TNF family BAFF and other molecules involved in plasma cell development. The airway mucosa of polyps has been shown to express inducible lymphoid tissue, follicle-like structures, and all required regulators of class switch recombination, including AID, RAGs, and others. Local receptor revision and class switching are clearly evident in CRSwNP, but not CRSsNP. [64,65,66,67,68]

2. IMMUNOGLOBULIN SYNTHESIS

The presence of bacteria in the nose and paranasal sinuses is well known, despite the fact that the cause of the inflammation linked to CRS is still unclear. However, there is a great deal of variation in the kinds of infections found, mostly because of the time period, sample collecting method, treatment strategies, and bacterial culture techniques. Bacterial colonisation is thought to worsen a non-infectious inflammatory response in CRS without underlying infection through bacterial allergy pathways. Superantigens can activate subpopulations of T-lymphocytes (5–30%), and bacteria like *Staphylococcus aureus* can elicit exotoxins. Bacteria-specific IgE has been found in 57% of patients with CRS compared to just 10% in subjects with allergic rhinitis. Common chronic eosinophilic-lymphocytic respiratory mucosal illnesses depend on bacterial superantigens in the pathophysiology of CRSwNP, superantigen generation, and host T-lymphocyte response. and nasal polyp tissue has been found to have staphylococcal superantigen-specific IgE antibodies to the superantigens SEA and SEB. [69,70,71,72,73]

A link with the comorbidity of asthma is suggested by the existence of SE-IgE antibodies and the rise in local IgE. In contrast to the allergic nasal mucosa, we

(Kimura et al.) have recently shown elevated expression of Thymic Stromal Lymphopoietin (TSLP) in nasal polyps, regardless of the atopic status, and that TSLP expression was positively correlated with eosinophils and IgE in the nasal polyps. Although IgA's function in the pathophysiology of CRS is uncertain, the fact that it is present in patients with the majority of chronic mucosal inflammations, including periodontitis, indicates that IgA is significant and may help define a distinct endotype of CRS. An anti-IgE approach has demonstrated encouraging treatment promise in nonatopic patients with nasal polyps and asthma, and recent research suggests that superantigens may be causative agents in the intrinsic form of severe asthma. These results should result in a novel understanding of the function of IgE "above atopy" and a clinically meaningful Endo typing of individuals with upper and lower airway illness.^[69,70,71,72,73]

3. INFECTIONS, MICROBIOME

Although there is strong scientific evidence that acute rhinosinusitis is primarily caused by an episodic viral infection of the paranasal sinuses, there is less evidence to support the idea that infection plays a major role in the pathophysiology of CRS. Infectious exacerbations brought on by viral infections are probably the cause of acute CRS exacerbations. Initially, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* were identified as common microorganisms associated with acute rhinosinusitis. A mixed bacterial infection containing anaerobic agents such *Prevotella*, *Fusobacterium*, and *Pepto streptococcus* species predominated as patients moved into the chronic phase. This data shows that the bacteriology of CRS patients differs from that of control patients prior to CRS acquisition. It is reasonable to state that bacteria are commonly found in the context of CRS; the paranasal sinus flora appears to be changed, with a higher prevalence of anaerobes and *Staphylococcus* species. This flora may show notable drug resistance and is frequently polymicrobial. Additionally, a study that looked at the microbiology of recurrent infected rhinosinusitis following endoscopic sinus surgery has been published. The findings further suggests that bacteria may produce symptoms even in patent sinuses, supporting the idea that bacterial infection might cause symptoms even after endoscopic sinus surgery. As a result, it is very likely that bacteria play a role in the pathophysiology of CRS. The extent of that involvement is still unknown. The aetiology and pathogenesis of CRS have also been linked to bacterial biofilms. Communities of bacteria enclosed in a protective extracellular matrix form biofilm, which are extremely ordered structures. Bacterial biofilm formation on surfaces like the sinonasal mucosa is an example of a universal survival strategy in less-than-ideal growth conditions. Through the sporadic release of free-floating planktonic bacteria, biofilms are thought to be a source of recurring exacerbations in CRS. They protect bacteria from both host defence and antibiotics. Using surgical samples, several

investigations have verified the existence of bacterial biofilms in the sinonasal cavity of CRS patients. In 30–100% of these samples, bacterial biofilms have been found using a variety of techniques.^[74,75,76,77,78,79]

DIAGNOSIS

Serious illnesses that resemble CRS can be ruled out with a negative physical check. A nasopharyngeal mass may be indicated by unilateral otitis media with effusion. Concerns about a sinus cancer are raised by facial numbness. A rhinosinusitis consequence is indicated by facial puffiness or difficulty moving the eyes. Routine CRS is not linked to fever or swollen neck lymph nodes. Dental infections can cause sinusitis, even though the majority of cases are rhinogenic in character. A sinus infection is strongly indicated by post-nasal discharge that seems purulent.^[34,35,36,37]

Nasal obstruction is the most prevalent symptom. Patients with nasal polyposis may have hypoxia, hypercapnia, snoring, sleep disturbances, and an elevated risk of hypertension. Loss of smell may result from polyps obstructing airflow to the olfactory cleft. Although nasal polyps are rare in children, they should be evaluated for cystic fibrosis. In adults, a unilateral nasal polyp should raise the possibility of an inverted papilloma or tumour; in children, it should increase the possibility of dermoid cysts, encephaloceles, and gliomas. In situations of antrochoanal polyps or postnasal drips associated with concurrent sinusitis, an examination of the oral cavity may reveal polyps behind the free edge of the soft palate.^[34,35,36,37]

Diagnosis can be done by

1. FIBEROPTIC NASAL ENDOSCOPY

A diagnostic procedure called fiberoptic nasal endoscopy produces fine-grained pictures of the nasal passageways and sinus chambers. Inflammation, a slow mucus outflow from the sinuses, a deviated septum, enlarged turbinate, or nasal polyps are some of the symptoms and possible causes of chronic sinusitis that it can reveal. A small fiberoptic device called an endoscope gives doctor a bright, clear picture of the whole nasal tube. The doctor may first use a local anaesthetic solution to reduce any discomfort during the treatment and a decongestant to open up the nasal passages before performing this procedure. The endoscope is then inserted through each nostril by the physician. The operation is performed in doctor's office and takes only a few minutes.^[82,83,84,85,86]

2. CT SCAN

Computed tomography, or CT, scans are the most effective way to image the sinuses. The sinus CT scan is a simple test that takes no more than fifteen minutes to complete. To create a detailed image of the sinuses and nose, it uses sophisticated computer technology and x-rays. You need to take off all of jewellery, including necklaces, ear rings, hearing aids, and any artificial teeth, for this examination. These things have the potential to disrupt this type of imaging. The bed that may be slowly

dragged inside the scanner will then ask you to lie flat. When ENT doctors order a CT scan of the sinuses for chronic sinusitis, they do not inject a dye or contrast agent into your veins. If ENT surgeon is worried about a tumour in sinuses or nose, she/he can ask the radiographer to put an intravenous cannula in patient hand and give a contrast agent at the time of procedure. This is known as a sinus contrast-enhanced CT scan.^[82,84,85,86]

3. MAGNETIC RESONANCE IMAGING

MRI shows the location and behaviour of nuclei emitting MR signals, it is usually regarded as the greatest anatomic imaging method available. This is because it assesses not just the tissues, as CT does via the absorption of X-rays, but also their qualities. Actually, MR has a greater contrast resolution, identifying the distinctions between two arbitrarily similar but not identical tissues by their varied relaxation periods (T1 and T2) and proton densities, whereas CT uses spatial resolution to separate two structures. Gadolinium, a chelate contrast agent whose seven unpaired electrons provide a very high magnetic moment, can be used to obtain contrast-enhanced T1-weighted images when necessary. This improves the identification of local illness extent and its diffusion beyond the paranasal sinuses. These MR capabilities offer a very thorough evaluation of soft tissues, including their differentiation and composition in fluids. This is very helpful in determining the features and level of inflammation, which is particularly crucial in CRS. Because MR can detect a much lower signal intensity on T2-weighted images and a lowered signal intensity on T1-weighted images, it is highly helpful in treating chronic fungal sinusitis. The ability of MR to discriminate sinus opacification brought on by inflammation or neoplasms by separating soft tissue from thick secretions is another benefit of MR over CT. This is accomplished by using T2-weighted images to identify the high signal of secretions in contrast to the intermediate signal of neoplasm.^[82,84,85]

TREATMENT OPTIONS

Topical steroids, adjuvant nasal rinsing, and optional systemic steroids and antibiotics make up the fundamental treatment for simple CRS, also known as "appropriate medical therapy".^[88,89,90,91,92,93,94,35,95,96]

1. TOPICAL CORTICOSTEROIDS

The first-line treatment for CRS is topical corticosteroids. It has been demonstrated that long-term use of topical nasal steroid sprays can relieve CRS symptoms and lessen sinus inflammation and nasal polyp growth. Short courses of oral steroids are used to treat CRS with nasal polyps, but they can also be used to treat severe CRS when quick symptom relief is required. Steroids applied topically and systemically promote eosinophil apoptosis and decrease mucosal eosinophil chemotaxis. Through a number of processes, corticosteroids also reduce the migration of white blood

cells, the generation of inflammatory mediators, the formation of antibodies, the release of histamine, and oedema. While long-term systemic steroid use is linked to serious adverse effects, daily topical nasal steroid use seems to be associated with little concerns. Consequently, acute CRS flare-ups or the postoperative phase following sinus surgery are the most typical times to administer a tapering course of oral steroids.^[97,98,99,100,101,102,103]

2. TOPICAL NASAL STEROIDS

For the treatment of CRS, topical nasal steroids have been frequently recommended. Topical corticosteroids have been shown in numerous studies to be effective in treating the symptoms of rhinitis and small to medium-sized polyps. Effectiveness in reducing symptoms during acute exacerbations was also shown when paired with antibiotic usage. Although the effect for nonpolypoid CRS has been more difficult to prove, corticosteroid nasal sprays have been demonstrated to postpone the recurrence of polyps following surgery. Nasal discomfort, mucosal bleeding, and crusting are common side effects of nasal steroids.^[97,98,99,100,101,102]

3. NASAL IRRIGATION

Patients tolerate nasal irrigation well, and there is no indication of any serious negative side effects. Increased ciliary beat activity, the elimination of antigen, biofilm, or inflammatory mediators, and a protective effect on the sinonasal mucosa are additional potential advantages of nasal saline irrigation. After endoscopic sinus surgery, nasal irrigation is very helpful for removing heavy mucus and crusts that are frequently left behind. The secondary prevention of exacerbations of rhinosinusitis may also benefit from daily saline irrigation.^[91,104]

3.1 Steroid nasal irrigation

In order to alleviate sinus inflammation, nasal irrigation has been supplemented with budesonide respules. It has been demonstrated that people with allergic rhinitis and CRS benefit from using budesonide as an aqueous nasal spray. The idea behind using budesonide respules for irrigation is that far larger steroid concentrations than those seen in prescription nasal steroid sprays can be applied topically to the sinus mucosa. steroid nasal irrigation with budesonide as a promising new therapy for select patients with CRS.^[105]

4. TOPICAL ANTIBIOTIC THERAPY

Delivering high concentrations of antibiotics directly to the site of illness with little systemic absorption and adverse effects is the aim of topical antibiotic therapy. Up to 30% of endoscopically guided cultures show methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas* aggravation of CRS following endoscopic sinus surgery. These infections can cause nasal polyps, altered sinonasal ciliary function, and chronic mucosal inflammation. They are also notoriously difficult to treat. Patients with CRS may benefit from topical treatment with antibiotics such as gentamicin or tobramycin to lessen

pain, mucosal oedema, secretions, and postnasal drip, particularly following endoscopic sinus surgery.^[106,107]

5. TOPICAL AND SYSTEMIC ANTIFUNGAL THERAPY

Oral itraconazole has been used as an adjuvant treatment for allergic bronchopulmonary aspergillosis (ABPA), and there is strong anecdotal evidence that some people with nasal polyposis and CRS may benefit from this as well. Itraconazole has been demonstrated to reduce the requirement for oral steroids, lower IgE levels, and improve symptoms, exercise tolerance, and lung function in ABPA patients. For some patients with allergic fungal sinusitis (AFS) and nonallergic eosinophilic fungal sinusitis, conditions thought to be comparable to ABPA, oral antifungals have been suggested as a therapy option.^[108,109,110,111]

6. TARGETED BIOLOGIC THERAPIES (MONOCLONAL ANTIBODIES)

Human antibodies known as biologics are made to attach to pro-inflammatory cytokines or inflammatory mediators in order to lower the immune response and chronic inflammation. For the treatment of severe bilateral CRSwNP, three drugs—dupilumab (anti-IL-4/IL-13), mepolizumab (anti-IL-5), and omalizumab (anti-IgE)—have been approved as an adjuvant to topical steroids in cases where systemic corticosteroids and/or surgery (dupilumab, mepolizumab) or intranasal corticosteroids (omalizumab).^[90,92,93,94,35,96]

Biologics are recommended for the treatment of severe bilateral CRSwNP following prior sinus surgery if at least three additional requirements are satisfied, according to the European position paper/EUFOREA.^[90,92,93,94,35,96]

1. indicators of type 2 inflammation (elevated total IgE, eosinophilia in tissue and/or serum).
2. Contraindications to systemic steroid therapy or the requirement for systemic steroid delivery.^[90,92,94,35,96]
3. Significantly reduced quality of life.
4. Significantly diminished perception of smell
5. Comorbid bronchial asthma. There are currently no biomarkers that can favour one biologic agent over another or predict the outcome of biologic therapy. Biologics have been shown in randomised, placebo-controlled trials to improve quality of life, reduce polyp size, and relieve symptoms. One of the following options should be chosen when the treatment's results are evaluated after six months.^[90,92,94,35,96]

1. ongoing therapy
2. supplementing the management of co-occurring conditions
3. Changing to a different biology
4. supplying extra surgical care
5. stopping therapy.

Biologics are expensive and require a lengthy course of treatment. According to the Red List, which was

retrieved on June 16, 2024, the annual cost per patient is 15 776.80 euros for dupilumab, 14 927.68 euros for mepolizumab, or 3654.72–27 413.92 euros for omalizumab. The question of whether and under what circumstances it is possible to extend the time between medication doses without decreasing treatment efficacy still needs to be answered. Side effects related to the new indication for usage should be highlighted, even though the approved trials indicate that the biologics are well tolerated. Injection-site responses (redness, itching, swelling), conjunctivitis, arthralgia, myalgia, rash, headache, and exhaustion are the most frequent.^[90,92,93,94,35,96]

OTHER TREATMENT OPTIONS

Decongestants

Decongestants are α -adrenergic agonists that cause the sympathetic nervous system to produce norepinephrine, which causes the nasal vasculature to contract. Although they are used to relieve nasal congestion, no research has shown that sinusitis resolves more quickly. Topical decongestants alleviate symptoms, although decreased mucosal blood flow may worsen ciliary loss and inflammation.^[97,98]

Mucolytics

A mucolytic can also enhance mechanical drainage. The most used drug for thinning mucus discharges is guaifenesin.^[97,98]

Antihistamines

Competitive blocking of histamine receptor sites on respiratory mucosal cells is how antihistamines function. Sneezing, watery rhinorrhoea, and face itching are the symptoms that atopic patients respond well to histamine type 1 blockers. For allergic rhinitis, antihistamines are the primary line of treatment. With fewer sedative anticholinergic effects, second-generation antihistamines have a greater affinity for the histamine receptor. Topical nasal second-generation antihistamines such as azelastine have also shown anti-inflammatory and mast cell-stabilizing qualities.^[97,99,100,101,102,103]

Leukotriene Inhibitors

Systemic drugs called leukotriene inhibitors are used to treat allergic rhinitis and asthma. The medications prevent smooth muscle contraction, chemotaxis, and enhanced vascular permeability caused by leukotrienes. Antileukotriene medication may help patients with CRS who have nasal polyps, as evidenced by the finding that leukotriene levels are elevated in the nasal secretions of individuals with asthma who are aspirin sensitive and have nasal polyposis.^[97,98,100]

SURGICAL TREATMENT FOR CRS

Surgery is typically only necessary for patients with CRS who do not respond to medication treatment. However, up to 50% of patients with CRS (not acute sinusitis) will eventually need surgery in some patient populations. The most frequent causes of surgical surgery include

symptomatic nasal polyp illness that cannot be effectively treated with medication alone and CRS that does not respond to medical management. However, a number of additional illnesses, such as mucocoele, allergic fungal sinusitis, and complex acute sinusitis, may necessitate surgery. Intranasal, sinus, and skull base tumour removal; closure of skull base defects; orbital decompression; dacryocystorhinostomy; and resection of medially positioned intraorbital lesions are only a few of the recent justifications for this sinus surgery that go far beyond inflammatory causes. Endoscopic intranasal intervention has nearly entirely replaced open surgery for CRS, which used to be primarily focused on mucosal stripping within the maxillary or frontal sinuses or ethmoidectomy carried out with restricted visualisation. Compared to earlier surgical techniques, FESS is linked to much lower morbidity and higher success rates, and the methods for doing such surgery are still developing. The effectiveness of prolonged approaches to the frontal sinus, utilising angled drills and intranasal instrumentation to achieve a partial septectomy and one big bilateral intranasal opening, has been shown in more recent studies.^[89,112,113,114]

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