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Review

Pathogenesis, Diagnosis, and Treatment of Infectious Rhinosinusitis

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Abstract: Rhinosinusitis is a common inflammatory disease of the sinonasal mucosa and paranasal sinuses. The pathogenesis of rhinosinusitis involves a variety of factors, including genetics, nasal microbiota status, infection, and environmental influences. Pathogenic microorganisms, including viruses, bacteria, and fungi, have been proven to target the cilia and/or epithelial cells of ciliated airways, which results in the impairment of mucociliary clearance, leading to epithelial cell apoptosis and the loss of epithelial barrier integrity and immune dysregulation, thereby facilitating infection. However, the mechanisms employed by pathogenic microorganisms in rhinosinusitis remain unclear. Therefore, this review describes the types of common pathogenic microorganisms that cause rhinosinusitis, including human rhinovirus, respiratory syncytial virus, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Aspergillus species*, etc. The damage of mucosal cilium clearance and epithelial barrier caused by surface proteins or secreted virulence factors are summarized in detail. In addition, the specific inflammatory response, mainly Type 1 immune responses (Th1) and Type 2 immune responses (Th2), induced by the entry of pathogens into the body is discussed. The conventional treatment of infectious sinusitis and emerging treatment methods including nanotechnology are also discussed in order to improve the current understanding of the types of microorganisms that cause rhinosinusitis and to help effectively select surgical and/or therapeutic interventions for precise and personalized treatment.

Keywords: fungi; bacteria; virus; rhinosinusitis; immunology

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1. Introduction

Rhinosinusitis (RS) is an inflammation of the mucosa of the nose and paranasal sinuses. RS affects about 15% of the population annually worldwide and has a high incidence and disease burden, which adversely affects quality of life [1–3]. The onset and development of RS are facilitated by infection as well as genetic and environmental factors. Based on duration, there are three types of RS: acute, subacute, and chronic (ARS, SRS, and CRS, respectively) [4]. ARS refers to any short-term (<4 weeks) persistent inflammation of the lining of the nose and sinuses. The most common cause of ARS is infection, primarily from viruses, but it can also be caused by bacteria and fungi. The duration of SRS is typically 4 to 12 weeks but sometimes more [1,4]. ARS was responsible for about 21.4 million outpatient visits from 2006 to 2010, while about 47.9 million visits were associated with a primary diagnosis of CRS, of which antibiotics were administered in 85.5% and 69.3% of ARS and CRS patients, respectively [5]. Another survey revealed that more than 80% and 50% of patients with ARS and CRS, respectively, were treated with antibiotics [6,7]. Clinical suspicion of infection is the foundation for the diagnosis of CRS. In this review, infectious RS is specifically defined as the acute exacerbation of RS caused by identifiable

infectious pathogens. Figure 1 illustrates the classification of infectious RS. Although the mechanisms by which pathogens cause RS are not completely understood, this review aims to elucidate the roles of viruses, bacteria, and fungi in RS pathogenesis and clarify the clinical characteristics, host immune responses, diagnosis, and treatment strategies to provide alternative viewpoints for the clinical diagnosis and treatment of infectious RS. As far as we know, this review is the first to focus systematically on the various pathogens that cause RS, summarize the diagnosis of different types of infections with RS, and discuss emerging treatments.

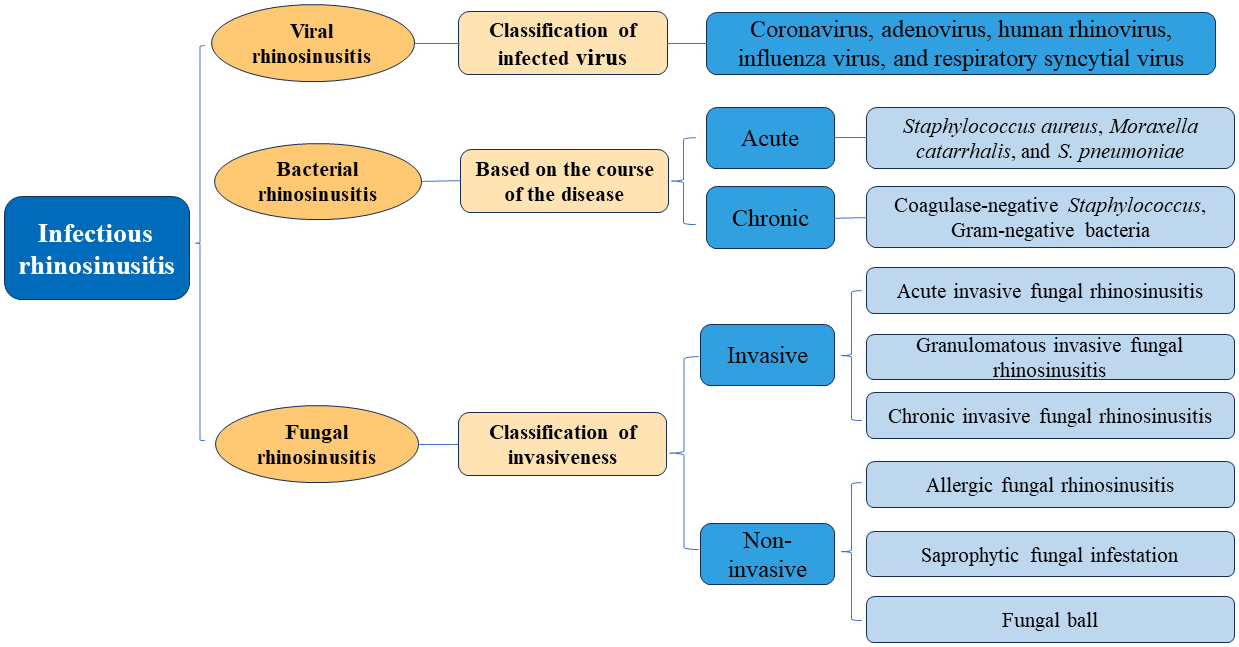


Figure 1. Classification of infectious rhinosinusitis.

2. Viral RS

Upper respiratory tract infections most often result from viruses and most cases resolve spontaneously. However, CRS is usually caused by upper respiratory tract infection, with progression of symptom severity and duration. Respiratory viruses are detected in mucosa or lavage fluid of about 50–70% of CRS patients [8,9]. Moreover, viral infection causes obstruction of the sinus opening, production of inflammatory mediators by nasal epithelial cells (ECs), damage to ECs and cilia, sustained changes to local cytokine production, and increased bacterial adhesion to nasal ECs [10]. A virus binds to the sinonasal epithelium through specific receptors, then enters the cell and replicates. Viral infection may be related to the sustained high reactivity of sinus mucosa and susceptibility to bacterial infections. In addition, viral infection triggers an immune response and upregulation of genes associated with airway remodeling, thereby exacerbating CRS [11]. Chronic inflammation, a decrease in mucociliary clearance, and a loss of epithelial barrier (EB) function are characteristics of the host immunological response to viral infection [12].

Coronavirus, adenovirus, human rhinovirus (HRV), influenza virus, and respiratory syncytial virus (RSV) are the most common causes of RS. HRV typically infects the upper respiratory tract. There are more than 160 HRV serotypes, which are classified into three groups: HRV-A, HRV-B, and HRV-C [13]. Interactions between the host genetics and HRV could have a significant impact on how severe RS is. Various clinical strains of HRV-A, HRV-B, and HRV-C are known to attack ECs at the gas–liquid interface of the paranasal sinuses. HRV-B strains replicate at significantly lower rates, promote a milder host immune response, and are less cytotoxic to cells than HRV-A and HRV-C, supporting clinical observations that HRV-A and HRV-C strains cause more severe disease than HRV-B

strains [14]. The second most frequent virus that causes sinus infections is RSV. In addition, although RSV infection is not age-specific, airway morbidity and mortality are significantly higher in infants, children, and the elderly due to damaged antiviral host responses [12].

These viruses attach themselves to nasal airway receptors that mediate cell entry, which triggers host immune responses. The presence of viral infection can lead to an inflammatory reaction, which can be identified by symptoms such as fever, nasal congestion, reduced sense of smell, face discomfort and/or pressure, and the discharge of mucus from the back of the nose. Respiratory viruses are commonly detected in CRS individuals, with rhinoviruses accounting for about 60–70% of CRS cases (11). However, viral upper respiratory tract infections can progress to bacterial RS and exacerbate CRS [8,9,15]. In addition, HRV infection can disrupt the microbial composition of the airways. For example, HRV infection leads to increased proportions of *Dolosigranulum* and *Moraxella* [16]. Meanwhile, rhinovirus infection can significantly alter the expression of C-C and C-X-C family genes, which control the recruitment of inflammatory cells.

2.1. The Pathogenesis of Viral RS

Viruses can play three distinct roles in the development of inflammation in CRS: initiating the inflammation, continuously stimulating the inflammation, and causing the sudden worsening of symptoms [10]. However, the specific roles of various viruses in RS remain unclear.

2.1.1. Virus-Specific Binding to Host Receptors

Respiratory viruses are transmitted through the mucosal surface of the nose or mouth via binding of the fusion protein on the viral envelope to nasal ECs through specific cell surface receptors. HRVs invade host cells through three cell membrane glycoproteins: intercellular adhesion molecule-1 (ICAM-1), low-density lipoprotein receptor (LDLR), and cadherin-related family member 3 (CDHR3) [17]. ICAM-1 is an immunoglobulin superfamily member that is expressed by endothelial cells, leukocytes, and ECs. It facilitates leukocyte adherence to endothelial cells as well as EC migration, barrier function, and proliferation [18,19]. The LDLR family members are a set of cell surface receptors involved in endocytosis that specifically bind to ligands found outside the cell. Cadherins are a cluster of glycoproteins that are embedded in the cell membrane and have a role in cell adhesion, cell signaling, and mechanical transduction. CDHR3 receptors exhibit a significant level of expression on the plasma membrane of airway epithelial cells [20]. A single nucleotide polymorphism (rs6967330) of *CDHR3* was reported to promote HRV-C infection and the occurrence of infantile diseases, thereby affecting the developing lung and increasing the risk of asthma. The rs6967330 allele was linked to increased HRV-C binding, replication, and total protein expression [17,21]. Moreover, the rs6967330 single nucleotide polymorphism is associated with a two-fold increased risk of CRS [22].

RSV enters cells by attaching to the CX3CR1 receptor on the heparin sulfate proteoglycan of airway cells through an attachment glycoprotein (G protein) [23]. The RSV F protein adheres to nucleolin, insulin-like growth factor-1 receptor, epidermal growth factor, and ICAM-1 before entering the cell [24]. The hemagglutinin (HA) protein of influenza viruses binds to sialic acid-containing receptors on various cell types, including the airways. In addition, influenza viruses cause red blood cell agglutination through hemagglutinin, a viral attachment protein. Influenza viruses also produce the surface protein neuraminidase, which cleaves sialic acid after binding to any molecule that does not cause viral infection, thereby releasing the virus. Influenza viruses target human airway ECs primarily through α-2,6 receptors [25]. Moreover, different coronaviruses bind to epithelial cells by different receptors. Human coronavirus HCoV-229E invades cells through human aminopeptidase N [26]. Angiotensin-converting enzyme 2 (ACE2) is used by the severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 to enter cells [27]. The high expression and broad distribution of TMPRSS2 in human organs help to active the SARS-CoV-2 spike protein and facilitate cellular entry and virus-cell fusion [28,29]. Angiotensin (Ang) II

is catalyzed and inactivated by ACE2, and tissue damage is encouraged by Ang II through inducing vasoconstriction, cytokine production, and apoptosis [30]. Nasal epithelial cells exhibit a significant expression of ACE2 [27]. HRV infection increases the expression of ACE2 in individuals with asthma [31], suggesting that HRVs, RSVs, and influenza viruses may also increase the expression of ACE2 and the harshness of coronavirus disease 2019 (COVID-19). However, further evidence is required to confirm this hypothesis. Investigations have revealed that individuals with CRS have a higher chance of contracting SARS-CoV-2 and developing severe COVID-19 [32]. ACE2 expression was elevated in nasal tissue of non-eosinophilic CRS patients [33,34].

2.1.2. Impairment of Ciliary Clearance and EB Destruction

Mucosal cilia clearance and EB function play important roles in resisting viral invasion. Mucus produced by goblet cells and submucosal glands clear the trichoid motile cilia lining the airways [35]. SARS-CoV-2 infection results in a transient decrease in EB function, the disruption of tight junctions (TJs), and the impairment of motile ciliary function [36]. Infection with respiratory viruses downregulates the expression of key genes involved in intrafilial transport and ciliary dynein machinery [37]. SARS-CoV and SARS-CoV-2 can destroy motor cilia by downregulating *FOXJ1*, a transcription factor necessary for cilia [29]. Prior investigations using experimental models have confirmed that influenza virus infection leads to the apoptosis of ECs, loss of ciliated cells, and thinning of cell thickness [38]. In addition, RSV can cause increased ciliary dyskinesia, accompanied by cilia loss and epithelial damage, thus leading to a substantial decrease in mucociliary clearance [39]. RSV viral surface glycoproteins can cause mucus production to rise and mucociliary clearance to slow down because they bind to the CX3CR1 receptor found on cell motile cilia and enhance the expression of mucins, such as MUC5AC and MUC5B [40]. It is very important that respiratory viruses and cilia-related processes interact. Why a prior viral infection makes the host more vulnerable to secondary coinfection with another pathogen is explained by the impairment of EC mucociliary clearance.

Zonula occludens-1 (ZO-1), occludin, and other TJ proteins that mediate paracellular transport and adherens junction formation make up the integral barrier of the airway epithelium. By attaching to the actin cytoskeleton, these proteins enable cellular integrity and intercellular adhesion. HRV infection leads to a significant reduction in mRNA levels of the components of TJs and adhesive connections [41]. RSV infection leads to the enhanced permeability of the airway epithelium and destruction of TJ structures, leading to airway barrier dysfunction [42]. Moreover, influenza viruses have been demonstrated to compromise the integrity of the airway epithelium and disrupt the TJ protein ZO-1's connection between the actin cytoskeleton and the transmembrane protein occludin [43]. Prior investigations have confirmed that viral infections and/or colds, allergies, and asthma are substantial risk factors for early onset CRS and that destruction of the EB plays a key role in the pathophysiology of CRS [44–46].

2.1.3. Host Immune Imbalance

Viruses activate the host immune response via various mechanisms. The infection of ECs by upper respiratory viruses activate immune cells to release cytokines, which cause inflammatory changes to the infected area. In addition, viral infection and lymphocyte clearance can exacerbate epithelial damage [47]. The host cell's pattern recognition receptors are activated to start the innate immune response. Viral RNA can activate about 40 cytoplasmic receptors and Toll-like receptors (TLRs) on the cell surface. Following the activation of signal integrators by these pattern recognition receptors, the production of genes encoding for inflammatory cytokines and antiviral IFNs is encouraged [48,49]. All three types of IFNs can directly or indirectly mediate antiviral responses [50,51]. While IFN production is essential for innate immunity against viruses, there is evidence that it may also be important in chronic inflammation [51]. HRV infection of human nasal ECs induces the expression of CXC motif chemokine ligand (CXCL)-11, inducible protein-10, CXCL-9,

and RANTES, and activates TLR7 and RIG-I [52,53]. However, an in vitro investigation found that no difference in the generation of antiviral IFNs induced by HRV between the healthy group and CRS groups [54]. In addition, in CRS individuals, the expression levels of type I and III IFNs and IFN-stimulated genes are decreased, suggesting that IFN expression levels are inconsistent [55]. According to a study on asthma, those with asthma had lower baseline levels of IFN production, which led to increased viral replication and an inflated IFN response during an asthma attack [56].

Th2 are characterized by the recruitment and activation of mast cells, basophils, and eosinophils and increased production of immunoglobulin E (IgE) and ILs. A previous study showed that HRV infection prompted the production of IL-33 and subsequent secretion of the type 2 cytokines [57]. Likewise, it has been shown that RSV infection increases the levels of IL-4, IL-6, and IL-13 in children's nasal rinse [58]. In addition, it has been demonstrated that RSV infection raises the levels of IL-33 and IL-13 in hospitalized newborns as well as IL-33 type 2 intrinsic cells in newborn mice [59].

In summary, the disruption of the EB and immune responses renders the nasal mucosa more vulnerable to antigen exposure and activation, while increasing susceptibility of the epithelium to viruses, thereby promoting disease progression and increasing the likelihood of bacterial infection.

2.2. The Diagnosis and Treatment of Viral RS

Since symptoms are often non-specific, viral RS is mainly diagnosed based on clinical manifestations of sinus inflammation, sinus computed tomography (CT), and molecular detection technology. Methods used for the detection of viruses mainly include traditional virus culture and direct/indirect immunofluorescence assays, rapid antigen detection, and highly sensitive nucleic acid amplification [60]. Rapid virus detection culture facilitates the detection of adenoviruses, influenza viruses, and RSV within 48 h [61]. The rapid direct antigen test is simple to perform but limited for the detection of influenza viruses and RSV [62,63]. The viral detection techniques with their advantages and disadvantages are shown in Figure 2. Since most cases of RS are acute, treatment is usually limited to antiviral drugs and surgery. In addition to the usual use of antiviral drugs, there are some emerging therapies. Ozone has been reported to inactivate both herpes simplex virus type 1 and the hepatitis C virus, and combined treatment with ozone and antiviral drugs has shown a reduction in inflammation and lung damage [64,65]. Antiviral antibodies made in a recovering patient's plasma are injected into the patient as part of convalescent plasma treatment. The treatment has shown efficacy in H5N1 influenza and Ebola virus disease, as well as improved cases of severe COVID-19 [66–69]. Research has confirmed a greater advantage for nanotechnology-based drug delivery in treating mice infected with SARS-CoV [70,71].

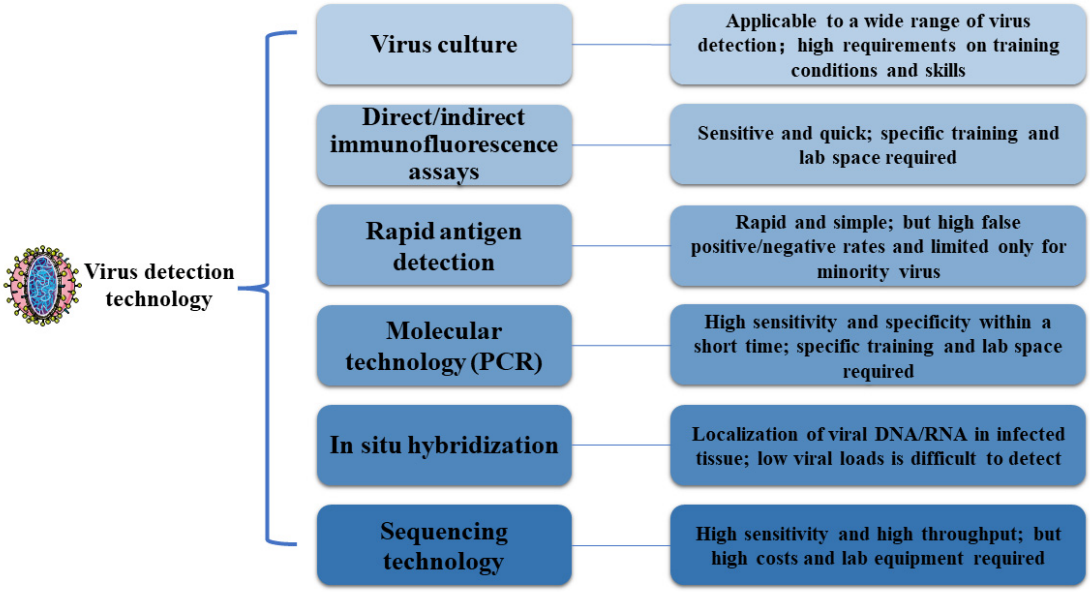


Figure 2. Comparison of several different detection techniques for viruses.

3. Bacterial RS

Bacterial RS is an infection of the nasal epithelium and paranasal sinus mucosa, usually caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.* Bacterial RS can be categorized as acute or chronic based on how the illness progresses. The differences between acute and chronic bacterial RS mainly include the following points: the duration of acute bacterial RS is generally not more than 12 weeks, while the duration of chronic bacterial RS is longer, mostly more than 3 months. Generally, chronic bacterial RS is more common than acute bacterial RS. The most common bacteria are *Staphylococcus aureus*, *Moraxella catarrhalis*, and *S. pneumoniae* in acute RS. Coagulase-negative *Staphylococcus*, Gram-negative bacteria, and anaerobic bacteria are the major causes of chronic bacterial RS. *Pseudomonas aeruginosa* is reportedly more common in those who have a history of sinus surgeries [72]. Moreover, sinonasal colonization by these bacteria can exacerbate inflammation.

3.1. The Pathogenesis of Bacterial RS

3.1.1. Bacterial Invasion of the Epithelium

In the initial phases of infection, bacteria disrupt mucosal barrier function by decreasing ciliary irritability and the frequency of basal cilia beats. Various virulence factors generated by *S. aureus* can effectively evade the host immune response while activating non-specific inflammatory responses. In addition, bacterial exo-proteins have been shown to disrupt EB function via downregulation of genes encoding transmembrane proteins [73]. Bacterial exo-proteins also disrupt the function of TJ proteins, resulting in the increased permeability of polarized ECs and could also directly or indirectly induce proinflammatory cytokines to disrupt the structural integrity of TJs and the EB. For example, *S. aureus* releases various exotoxins, including toxic shock syndrome toxin 1, *Staphylococcus* enterotoxins, and *Staphylococcus* superantigen-like toxins [74]. Moreover, staphylococcal enterotoxin B (SEB) exhibits superantigen properties that directly affect immune stimulation via the recruitment of effector cells and the generation of inflammatory cytokines. In addition, SEB upregulates the production of IL-6 by activating TLR2 [73]. As a possible mechanism of SEB, mast cells ingest *S. aureus* for degradation. However, non-degraded but active *S. aureus* combined with SEB stimulates the degranulation of mast cells and release pro-inflammatory mediators and cytokines [75]. Moreover, SEB induces the production of reactive oxygen species (ROS) in the ECs of CRS patients. The exposure of nasal ECs to SEB increases the production of mitochondrial ROS. In fact, inflammation is associated

with the generation of ROS, which is related to the induction of endoplasmic reticulum stress and the development of nasal polyps [76–78]. Similarly, elastase and serine proteases released by *P. aeruginosa* has been correlated with increased permeability, decreased transepithelial electrical resistance, and the severity of CRS [79–81]. The transmembrane proteins tricellulin, occludin, and claudin-1 and -4 were reduced by the elastase, which also damaged the epithelial barrier. Additionally, *P. aeruginosa* elastase decreased PAR-2 expression, which in turn controlled the production of TJ proteins [82]. Bacterial biofilms can significantly damage the sinonasal cilia and are found in the sinuses of about 42–80% of CRS patients [83]. Moreover, biofilm formation plays a role in the severity and persistence of CRS and the failure of antibiotic therapy [84]. Oral antibiotics are difficult to use against deep bacterial biofilms, and systemic high concentrations of drugs may be toxic and also affect commensal microorganisms and cause resistance to antibiotics [74,85].

In addition, the breakdown of the epithelial barrier and dysregulation of mucin expression are hypotheses of biofilm involvement in CRS formation [86]. When the epithelium barrier is destroyed, the body is exposed to more microbes, and inflammatory reactions are overstimulated. Multiple mucins in CRS are dysregulated in their expression, and these mucins serve as bacterial adhesin attachment ligands, triggering bacterial colonization [87]. The incidence of bacterial biofilm in CRS is significantly higher. Moreover, the expression level of MUC5B is increased, indicating a certain relationship between biofilm and mucin expression [88]. The most often detected bacteria that form biofilms in CRS individuals include *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *P. aeruginosa*. Bacterial biofilms are also detected in healthy groups, suggesting that biofilms could be a normal respiratory tract element [89]. However, other investigations have suggested that patients with CRS who develop biofilms may have a poor prognosis and disease resistance. For example, the quality of life of CRS individuals with bacterial infection and biofilm formation after functional endoscopic sinus surgery (FESS) was significantly improved at the initial stage, although there was no noticeable distinction in CRS patients without biofilm formation at 6 months after FESS [74,90]. Refractory CRS is defined by the increased recruitment of $CD4^+$ helper T cells and biofilm production by *S. aureus* [91]. In addition, the extracellular proteins of the *S. aureus* biofilm decrease transepithelial electrical resistance, increase cytotoxicity and permeability, and disrupt TJ proteins in a time- and dose- dependent manner. These alterations could lead to mucosal inflammation in CRS patients [92]. Moreover, biofilm produced by *S. aureus* is linked to eosinophil markers of inflammation, such as eosinophil cationic protein and IL-5, indicating the possible significance of staphylococcal biofilms in TH2 inflammation in chronic rhinosinusitis with nasal polyps (CRSwNP) [93].

3.1.2. Host Immune Response

The disruption of the nasal EB by virulence factors and other components of bacteria triggers an inflammatory response by the host cell. Bacterial virulence factors function as superantigens and can bypass processing by antigen-presenting cells and attach directly to major histocompatibility complex class II molecules and T cell receptors, thereby activating many T cells, accompanied by B cell proliferation and eosinophil activation [94]. The activation of B cells upregulates the expression of Th2 cytokine, causing the synthesis of polyclonal IgE and the release of histamine. Clinically, significant elevations of the key proinflammatory cytokines TNF-α, IFN-γ, and IL-13 were detected in inferior turbinate tissue supernatants of CRS patients with SEB, indicating the presence of a type 2 inflammatory phenotype [94,95]. In summary, bacteria increase the severity of RS mainly through biofilm formation and also regulate immune responses via the disruption of tissue barrier function and the impairment of mucociliary clearance, which promotes the development of polyps and type 2 inflammation [96].

3.2. The Diagnosis and Treatment of Bacterial RS

The main methods used to diagnose bacterial RS are sinus CT, clinical symptoms, and microbial culture. Viral and bacterial ARS are often followed by many common

cold symptoms, such as sore throat, cough, fever, and sinus irritation. Furthermore, the symptoms of bacterial ARS are generally worse than a common cold and may cause severe one-sided facial pain, high fever (>38°), and greenish yellow to rust brown mucus. Viral RS is generally acute, while the symptoms of bacterial RS are often longer lasting. The symptoms of severe or long-lasting CRS caused by an acute bacterial infection include nasal blockage/congestion, nasal discharge, altered sense of smell, and facial pain. For patients without sinus disease, the sinus spaces are full of air and will appear black on a CT scan. In CRSwNP individuals, on a CT scan, the sinus lining appears grey instead of black due to edema and inflammation, and the sinuses may appear partially or entirely filled with polyps or mucus [1].

Treatment options include topical intranasal steroids, oral antibiotics, topical antibiotics, nasal saline irrigation, oral steroids, or combinations of oral antibiotics and steroids. The matrix components of bacterial biofilms protect the bacteria from antibodies, phagocytosis, and antibiotic killing [97,98]. According to reports, individuals with CRS biofilm responded less well to high antibiotic dosages and experienced more FESS revisions [85,99]. In recent years, natural products have the advantage of being less toxic, and some researchers have reported the potential role of natural products in inhibiting bacterial biofilms; for example, honey and and active component of honey (methylglyoxal) significantly decreased *S. aureus* biofilm in a sheep sinusitis model [100]. Other natural products, including 1,8-cineole and xylitol, have also been used to prevent the development of regular sinonasal bacterial biofilms [101–103]. A higher concentration of NO can reduce the biomass of *S. aureus* biofilm isolated from CRS individuals [104,105]. In addition, it has been reported that phage therapy can overcome antibiotic resistance in chronic rhinosinusitis [106]. Although these new treatments have some effect on the clearance of CRS bacteria, additional clinical research is required to justify their wider use. Surgery is required for refractory cases, and immunoglobulin replacement therapy may be required for those with underlying immunodeficiency [107,108].

4. Fungal RS

Fungal RS is a general term describing fungal diseases of the nasal cavity and sinuses. The main predisposing factors of fungal RS are antibiotic use, corticosteroid treatment, and diabetes. In contrast to bacterial and viral RS, the most typical signs and symptoms of fungal RS include ocular swelling, exophthalmos, and headache [109]. Depending on the presence of pathogenic fungi, fungal RS is classed as invasive or non-invasive. Invasive fungal RS includes acute invasive fungal rhinosinusitis (AIFRS), granulomatous invasive fungal rhinosinusitis (GIFRS), and chronic invasive fungal rhinosinusitis (CIFRS). The symptoms of invasive fungal RS include fever, coughing, and sometimes nasal mucosal ulcers [110,111]. Histopathological studies show that fungal RS is characterized by hyphal invasion of the sinus mucosa, submucosa, and blood vessels with vasculitis, thrombosis, and tissue infarction [112–114]. This aggressive form is often seen in immunocompromised individuals, older people, and those with intracranial involvement, who usually have a poor survival rate. Non-invasive fungal RS includes allergic fungal rhinosinusitis (AFRS), saprophytic fungal infestation, and aspergilloma (fungal ball) [111,115]. Non-invasive fungal RS presents as CRS that does not respond to repeated antibiotics and surgery [116]. A retrospective study of 400 patients with fungal RS reported that 87.5% were non-invasive lesions, of which 40% were fungal spheroid, 45% were AFRS, 12.5% were invasive RS, and 11.0% were AIFRS. Moreover, *Aspergillus* was the most common fungus isolated from aspergilloma, AFRS, and AIFRS patients [117,118].

4.1. Invasive Fungal RS

4.1.1. AIFRS

AIFRS is a rare but deadly illness brought on by an invasive fungal invasion of the paranasal sinuses and nasal cavity. Fungal hyphae appear in the mucosa, submucosa, blood vessels, or bones of the sinus and subsequently spread into the orbit and brain within a

few hours [111,114,119]. The survival rate of AIFRS is only 20–80% [119–121]. Pathogens causing AIFRS include typical *Mucor*, *Aspergillus*, and atypical fungi (*Alternaria*, *Candida*, *Fusarium*, *Paecilomyces*, *Scedosporium*, and *Scopularopsis*) [122–124]. Previous investigations confirmed that susceptibility to AIFRS is increased in patients with host cell-mediated immune deficiency, especially neutropenia, hematological malignancies, aplastic anemia, hemochromatosis, poorly controlled diabetes, liver and kidney failure, acquired immunodeficiency syndrome, and organ transplantation, as well as those receiving immunosuppressive therapy with systemic steroids or chemotherapeutic agents [114,125,126]. An analysis of 807 individuals discovered that the most common symptoms of AIFRS include facial swelling, fever, nasal congestion, and orbital lesions in about half of patients, altered mental status and palate necrosis in a small percentage of patients, and enucleation of the eye in about 19.8%. Although antifungal medication and early surgical debridement are used in the treatment of most AIFRS patients, the overall survival rate is only 49.7%. However, individuals who received liposomal amphotericin B or had open or endoscopic sinus surgery had a higher survival rate. Reported poor prognostic factors include intracranial involvement, treatment delay, altered mental status, eye socket resection, advanced age, diabetic ketoacidosis, and drug resistance [116,127]. Therefore, early diagnosis and treatment are crucial to decrease the morbidity and mortality associated with AIFRS.

Pathogenesis and Host Immunity

Anatomical abnormalities, environmental exposures, microbial toxicity, genetic background, and immune state have all been suggested as underlying causes of AIFRS, even though the pathogenesis and etiology of the condition are still unknown. The type of nasal mycosis is primarily determined by immunological condition. Crucially, it is still unknown what pathophysiological pathways lead from harmless fungal colonization to fungal RS.

Diagnosis of AIFRS

Clinical symptoms: Common symptoms of AIFRS include acute nasal obstruction for a month or less, facial swelling, and fever. Other less common symptoms include facial pain/numbness, headache, eye paralysis and protrusion, changes to vision, and significant mental changes [122,128]. Maxillary involvement has been found to be significantly linked with mortality [129]. However, these symptoms are not specific and often overlap with other diseases and bacterial/viral RS.

Microbiological examination: Fungal species are considered important prognostic factors, with *Aspergillus* and *Mucor* as the most common causes of AIFRS [130]. Previous investigations reported that *Mucor* infection is predictive of worse outcomes. As compared to infections by *Aspergillus* and *Fusarium*, individuals with diabetes are more likely to have an infection with *Mucorales*. In addition, baseline creatinine levels are greater in patients with invasive fungal RS caused by *Mucorales* infection than in patients with *Aspergillus* and *Fusarium* infections [131]. Atypical fungal infections have been associated with a worse 1-month survival [124]. However, microbial culture is time-consuming, and only 36% of confirmed cases have positive culture results [132]. In addition, detecting fungal infections can be done using molecular biology methods, including real-time fluorescence quantitative polymerase chain reaction (PCR) for *Aspergillus* and *Candida*, and nested PCR for *Mucorales* [133]. A previous investigation reported that the culture technique alone detected fungal components in 25% of nasal lavage fluid samples, while the PCR technique alone found fungal DNA in 44% of nasal lavage fluid samples, whereas the positivity rate was improved to 50% by the combination of the culture and PCR techniques. Although PCR analysis significantly improved the fungal detection rate of nasal lavage fluid samples, the culture technique remains the gold standard [134,135]. In addition, the identification of blood-based fungal indicators such as galactomannan or β-glucan is important for diagnosing invasive aspergillosis; nevertheless, its specificity and sensitivity are restricted. Moreover, there was no noticeable difference in peak galactomannan levels of patients with positive versus negative pathological results for AIFS. False-positive results of elevated

galactomannan can occur due to various factors, such as diet, other fungi, and the use of certain antibiotics. Therefore, caution is recommended with the use of galactomannan to diagnose AIFRS [136].

Laboratory tests: Absolute neutropenia and diabetes mellitus are primary risk aspects for AIFRS. Therefore, dynamic monitoring of basal metabolism markers and assessment of blood glucose/ketoacidosis is important for diagnosing RS. Unexpectedly, increased glycated hemoglobin (HbA1c) was linked to better survival, possible because higher HbA1c is a more treatable and reversible cause of immunosuppression. However, further investigations are needed for confirmation [124]. Meanwhile, blood analysis is also required to assess the absolute neutrophil count (ANC). In a previous study, 82.9% of 41 patients with AIFRS had an ANC < 500/μL [128]. Although investigations have found no significant relationship of ANC < 500 μL with the diagnosis and prognosis of AIFRS, ANC < 500 μL remains an important risk factor for AIFRS [124]. Moreover, C-reactive protein levels are significantly associated with the survival of patients with AIFRS [129,137,138]. Therefore, it is important to closely monitor the indicators of acute inflammation.

Imaging and nasal endoscopy: CT and magnetic resonance imaging (MRI) are commonly used for the diagnosis of the sinuses. Through CT, AIFRS is characterized by the severe edema of the mucosa and soft tissues and thickening of the sinus mucosa. The most reliable CT result is unilateral nasal mucosal thickening, and these occur more frequently in immunocompromised than immunocompetent patients [139]. MRI is a more sensitive diagnostic method for AIFRS than CT. As an inherent advantage, the resolution of soft tissue contrast is better with MRI than CT. Therefore, MRI can more accurately distinguish mucus from edema when evaluating the intracranial and orbital infiltration of AIFRS. Signs of AIFRS described by MRI include inflammation of the orbital fat and extraocular muscles with leptomeningeal enhancement [140]. The most common findings of AIFRS by nasal endoscopy include pale or necrotic mucosa, strong necrotizing nasal crust, and clear or viscous mucus secretions. The most often impacted areas of AIFRS are the middle meatus and middle turbinate, which are followed by the nasal septum and inferior turbinate. Nasal endoscopy showed that necrosis was mostly unilateral, while bilateral necrosis was rare. Few patients had no changes via nasal endoscopy, while most had changes to bone mineral density and sinus opacities via CT [141]. Moreover, nasal endoscopy revealed modifications to the nasal mucosa. According to reports, mucosal edema is an early endoscopic observation that is followed by discoloration, when the pale pink mucosa is replaced with granulation and ulceration. Black discoloration is a sign of late AIFR tissue necrosis, whereas white discoloration is indicative of ischemia brought on by vascular invasion [122].

Histopathological detection: At present, the gold standard for diagnosing AIFRS is tissue biopsy. Traditional formalin-fixed, paraffin-embedded (FFPE) histopathological samples are typically stained with hematoxylin and eosin, periodic acid Schiff (PAS), and Gomori methylamine-silver (GMS) to verify fungal invasion of tissues. Nevertheless, the FFPE method is time-consuming and hinders the rapid diagnosis of AIFRS. For rapid diagnosis of AIFRS, many investigators have argued that frozen section biopsy should be used when evaluating patients who are considered to be at risk [142,143]. The sensitivity of frozen sections for the diagnosis of AIFRS has increased after the addition of modified PAS staining for fungi [144,145]. GMS staining of cryosections is a quick and dependable method for its accuracy, sensitivity, and specificity in diagnosing fungal invasion, with good accuracy when compared to the gold standard FFPE biopsies. Frozen section biopsy is therefore strongly advised for an efficient and quick diagnosis of suspected AIFRS.

Treatments of AIFRS

The three common methods for treating AIFRS are reversing the underlying immunodeficiency, antifungal medication, and early surgical debridement. The potential explanations for increased survival after surgery include the availability of culture specimens and earlier tissue diagnosis, penetration of antifungal therapy after resection of necrotic

tissue, reduction of fungal burden, and improved postoperative sinus monitoring. Most patients are advised to avoid irritating the necrotic sinus tissue prior to surgery [91]. The surgical strategy of bilateral FESS with debridement of the significantly involved area and antifungal therapy avoids repeat surgery for AIFRS without any change to efficacy [146].

Surgical management: The intranasal technique offers less invasiveness for individuals with poor circumstances and is appropriate for people diagnosed at an early stage of AIFRS. When there is palatal, intracerebral, or intraorbital involvement, open surgery is the better option [147]. However, open surgery did not improve survival, possibly because this patient group had more extrasinus infections. Nonetheless, the survival of patients with orbital or cerebral involvement was less than 6 months, regardless of the clearance of infectious invasive fungi. Intracranial and ethmoid sinus involvement was notably connected to the mortality of AIFRS, possibly due to an increased propensity for fungal infection of the ethmoid sinus, which often spreads directly to the orbit and anterior cranial cavity [148]. Additionally, those who had open surgery might have experienced necrosis and/or a more severe fungal burden. Although investigations have suggested that early endoscopic surgery is key to prognosis, increased time from diagnosis to treatment is an inverse predictor of mortality because patients with a longer onset of symptoms typically have more chronic diseases as compared to those who present with a more aggressive disease course [124]. However, timely diagnosis and treatment are only beneficial for improving morbidity, not mortality [149].

Medical management: Systemic antifungal treatment is also an effective treatment for AIFRS. Amphotericin B and liposomal amphotericin B are currently the main antifungal drugs for AIFRS with *Mucor* infection [141]. In a retrospective study, the survival rate differed among 77.5% and 15.0% of patients with AIFRS who received amphotericin B and liposomal amphotericin B, respectively [116,150]. Furthermore, a systematic review of zygomycosis found that surgery combined with amphotericin B significantly improved survival as compared to either amphotericin B or surgery alone [151]. In addition, an AIFRS patient with acquired immunodeficiency syndrome treated with the newly approved antifungal agent isavuconazole provides a reference for patients with invasive fungal RS either in refractory or intolerant to amphotericin B [152].

Reversal of immunodeficiency: An immune-stimulating therapy (IST) is designed to promote granulocyte, macrophage, and hematopoietic cell maturation. An IST is based on granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte infusion, and G-CSF combined with granulocyte infusion. In a systematic review, compared to 44% of untreated patients who died, 88.3% of patients treated with G-CSF survived [151]. Although routinely used for chemotherapy-induced neutropenia, the effectiveness of ISTs for specific opportunistic infections is uncertain. Moreover, an IST was found to significantly improve short-term survival, as determined by multivariate analysis [124]. In addition, it is said that restoring the neutrophil count is necessary to eradicate the infection [153].

4.1.2. CIFRS and GIFRS

The most prevalent invasive fungal RS is AIFRS, which is classified into two types: CIFRS and GIFRS. CIFRS is a relatively rare invasive fungal disease involving the paranasal sinuses and nasal cavity with an uncertain pathogenesis. Histologically, sparse inflammation, sporadic vascular infiltration, and extensive hyphae formation are the main features of CIFR [111]. As compared to AIFRS, CIFRS progresses slowly over a period of months to years [154]. A retrospective analysis found that compromised immunity, diabetes mellitus, and extended corticosteroid use are significant risk elements for CIFRS [155]. In another investigation, one or more predisposing factors were found in 43.1% of CIFRS patients [156]. Unlike AFIRS, the reversal of underlying immunodeficiency is not necessary for CIFRS, which also occurs in immunocompetent individuals. Clinical symptoms of CIFRS are nonspecific and may include facial pain, pressure, runny nose, nasal congestion, epistaxis, and symptoms related to the invasion of the orbit or brain [157]. *A. fumigatus*,

A. flavus, *Mucor*, and *C. albicans* are the frequent species causing fungal infection [158]. In addition, CIFRS caused by the rare fungi *Paecilomyces variotii* has also been reported [159]. CIFRS is histopathology characterized by the fungal invasion of sinus tissue, positive fungal culture, soft tissue infiltration, and irregular bone destruction detected via CT or MRI. The thickening of the sinus mucosa and sinus opacification are the most frequent CT findings [160].

Unlike CIFRS, granulomatous inflammation along with severe fibrosis is a characteristic of GIFRS. Large numbers of multinucleated giant cells and fewer numbers of epithelioid, lymphocyte, plasma, eosinophil, and neutrophil cells formed these noncaseating granulomas, while the presence of fungal hyphae is rare. According to reports, GIFRS is prevalent in hot, arid nations like Sudan, Pakistan, and India. *A. flavus* has been isolated from most granulomatous fungal RS [161].

Between CIFRS and GIFRS, there are no appreciable differences in survival rates, clinical profiles, or demographic characteristics. However, in the granulomatous group, the median time between the onset of symptoms and diagnosis was 4 months, a substantially greater duration than that in the chronic group [156]. Diagnosis and treatment are similar to AIFRS. Surgery and antifungal drugs are commonly used for the treatment of CIFRS and GIFRS. Similar to AFIRS, interventions include open surgery, endoscopy, and combined surgery with the use of antifungals [115].

4.2. Non-Invasive Fungal RS

4.2.1. AFRS

AFRS is a subtype of CRSwNP that is characterized by specific antifungal IgE production, eosinophil-rich mucus, and characteristic CT and MRI findings of the paranasal sinuses [162]. AFRS usually occurs in immunocompetent atopic persons, strikes more frequently in regions with warm temperatures and high humidity, impacts younger people (ages 21–33), and affects men more than women [163]. The most prevalent pathogenic fungi of AFRS are the *Aspergillus* species and dematiaceous fungi, including *Alternaria*, *Bipolaris*, *Cladosporium*, and *Curvularia* [162,164,165].

Pathogenesis and Host Immune Response

AFRS involves molecular signaling in antifungal immunity, mucosal barrier physiology, and fungal activation, which result in an excessive type 2 immune response featured by the production of the cytokines IL-4, IL-5, and IL-13, and upregulation of adaptive immune responses characterized by elevated IgE levels [166,167]. Previous investigations suggest that the characteristics of AFRS are pathogenic fungi, elevated IgE levels, and systemic allergy to fungal antigens [168–170]. However, recent investigations confirmed a high positive fungal culture rate for people with and without AFRS [171,172]. For both AFRS and CRS patients without a fungal allergy, there was no significant distinction in the levels of fungal-specific IgE or in the generation of fungal-specific peripheral lymphocytes. In addition, reactivity to fungal antigens and the presence of fungi-specific IgE and IgG can occur in both non-allergic and allergic fungal RS [173–175]. Immunohistochemical analysis of tissues from AFRS individuals and non-allergic eosinophilic fungal RS showed no variations in the numbers of mast cells and eosinophils [176].

Epithelial activation with concomitant EC apoptosis and loss of EB integrity: The EB of the nasal mucosa is composed of a group of cells, peptides, and proteins that are intricately connected to the immune response [163]. Alterations to EB function are considered important for the pathogenesis of AFRS. Decreased transepithelial electrical resistance has been observed in cultured sinus ECs from patients with AFRS. Moreover, the decreased expression of the TJ proteins occludin and junctional adhesion molecule-A and the increased expression of the leaky TJ protein claudin-2 were linked to increased epithelial permeability [177]. In addition, fungal proteases can cause structural changes to epithelial junctions and increase epithelial permeability [178,179]. In addition, the protein and peptide components of the natural barrier of the nasal mucosa, including defensins, an-

timicrobials, lysozyme, lactoferrin, and SPLUNC1, are also involved in the defense against pathogens and mucosal injury [180,181]. The expression levels of lactoferrin, surfactant protein, and antibacterial S100 protein, histatin-1, and histatin-3 are reduced in AFRS patients [182–185]. Therefore, immunodeficiency of antimicrobial peptides in AFRS patients results in increased susceptibility of the EB to fungi and decreased clearance of proteases and mycotoxins [181].

Release of proinflammatory chemokines and cytokines: The respiratory epithelium of the sinuses and lower airways releases innate inflammatory cytokines (also called epithelial-derived cytokines), including thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, which contribute to type 2 inflammation. TSLP induces the production of IL-5 and IL-13 by type 2 cells and type 2 intrinsic lymphoid cells (ILC2s). The ST2 receptor of IL-33 exists on eosinophils, T cells, innate lymphoid cells, and mast cells. IL-33, through the ST2 receptor, can promote Th2 polarization, eosinophil production, and type 2 inflammation [186]. IL-25, a distinct member of the IL-17 cytokine family, is also referred to as IL-17E [187]. Chemosensory cells (SCCs) are the main source of IL-25 in the human sinus epithelium [188]. As compared to normal controls, expression levels of SCCs and ILC2s are increased in CRS patients [189]. An elevated level of the IL-33 receptor in AFRS patients has been connected with the increased gene expression of eosinophils and mast cells [167].

Animal and cellular models have confirmed that epithelial-derived cytokines promote type 2 inflammatory responses. In asthma, TSLP and IL-33 cooperatively promote ILC2 activation and induce congenital allergic inflammation [190]. Airway ECs release IL-33, IL-25, and TSLP in a mouse model of allergic airway inflammation triggered by fungi. ILC2s then quickly produce type 2 cytokines, which cause airway eosinophilia, mucus formation, and hyperresponsiveness [191]. In a model, ILC2 was shown to significantly reduce TJ integrity via the expression of IL-13. In addition, epithelial electrical resistance was decreased and isothiocyane-dextran fluorescein permeability was increased, consistent with the decreased mRNA and protein expression of TJ proteins [192,193].

Another crucial aspect of type 2 inflammation is eosinophil activation. Mast cells and eosinophils are recruited and activated by IL-9 and IL-5, respectively. When IL-4 and IL-13 are present, B cells switch their class and start producing IgE. The specific IgE antibodies attach to basophil and mast cell surface high-affinity receptors [194]. In addition, eosinophils can release superoxide anions, hydrogen peroxide, and eosinophil peroxidase, which damage the ECs of the nasal mucosa [195]. The ratio of dendritic cells is increased in CRS individuals [196]. The production of CCL20 and CCL2 by nasal ECs in response to stimulation by other antigens, such as fungi, recruits immature dendritic cells from the peripheral blood. After stimulation with epithelial-produced TSLP, dendritic cells generate large amounts of CCL17, CCL18, and CCL22, which are involved in the Th2 cell recruitment process [197]. Mast cells are crucial initiators of inflammatory responses. After receiving allergen signals, mast cells promote vascular dilation and permeability by secreting pro-inflammatory chemokines and other molecules that promote the recruitment and trafficking of immune cells to the sites of infection and inflammation. These immune cells interact with each other to maintain and prolong inflammation [195,198,199].

Exposure to conditions that allow fungal spores to enter the sinuses, where the spores can germinate into immunogenic fungal hyphae and cause EB dysfunction as well as the release of TSLP, IL-25, and IL-33, epithelial-derived cytokines, is what causes AFRS. As a result, the type 2 immune response becomes compensatively overstimulated, triggering an inflammatory cascade that produces mucus, eosinophilia, and nasal polyps. The infiltration of various immune cells and the increased secretion of inflammatory mediators cause tissue edema and mucus production, which disrupt the EB and increase the risk of fungal invasion. This vicious cycle eventually progresses to AFRS [200–202]. There is a significant correlation between the obvious type 2 inflammation observed in AFRS and the disruption of innate immune signaling and EB function (Figure 3).

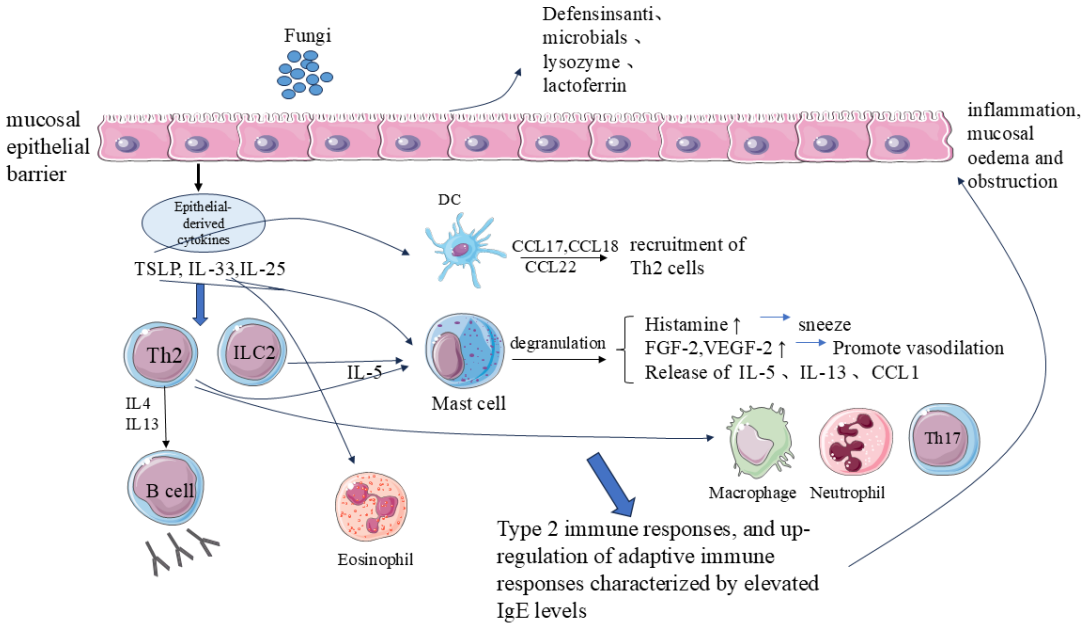


Figure 3. The immune response in AFRS. Fungal colonization in the nasal cavity and paranasal sinuses leads to epithelial cell activation followed by epithelial cell apoptosis and the loss of epithelial barrier integrity. Various proteins and peptides are released to defend against pathogens and mucosal damage, in addition to the increased production of epithelial-derived cytokines, including TSLP, IL-25, and IL-33. The subsequent inflammatory cascade leads to eosinophilia, formation of nasal polyps, and mucus production. Tissue edema and mucus production caused by the infiltration of various immune cells and increased secretion of a series of inflammatory mediators damage the epithelial barrier, leading to impaired fungal clearance and increased risk of invasion, which finally manifests as AFRS. Note: TSLP: thymic stromal lymphopoietin; IL33: interleukin 33; IL-25: interleukin 25; ILCs: type 2 intrinsic lymphoid cells; Th2: T helper 2 cell; Th17: T helper cell 17; IL-4: interleukin 4; IL-13: interleukin 13; IL-5: interleukin 5; DC: dendritic cell; FGF-2: fibroblast growth factor 2; VEGF-2: vascular endothelial growth factor receptor 2; CCL1: C-C Motif Chemokine 1. ↑: increased secretion or expression.

Diagnosis

Nasal polyps almost invariably accompany AFRS, which manifests as CRS symptoms unresponsive to traditional medical treatment. However, as compared to CRSwNP, the nasal discharge of AFRS patients is usually as thick as peanut butter with a greenish-brown mucoid appearance (Table 1).

Table 1. Differences between AFRS and CRSwNP.

	AFRS	CRSwNP	Reference
Secretions	Thick, peanut butter consistency	Thick	[1]
Serum IgE	High	Lower than AFRS	[203]
CT imaging	Opacification with hyperdense areas and central hyperattenuation due to allergic mucin	Opacification	[204,205]
Fungi	*Aspergillus* species and melanin-producing fungi	*Alternaria* and *Cladosporium*	[162,206,207]
HLA	HLA-DQB1*0301 and HLA-DQB1*0302 were highly correlated	HLA-DQB1*0301 and HLA-DQB1*0302 less prominent	[208]

Note: *: In HLA nomenclature, use an asterisk * to separate the gene from the 4 numeric regions.

The complications that may occur in AFRS patients include visual disturbances, exophthalmos, facial deformities, and intracranial sequelae, such as stress-induced intracranial neuropathy and intracranial abscesses. Sinus CT images of individuals with AFRS usually

display nearly complete opacity with heterogeneous radiation density of the sinus soft tissues. CT findings include sinus dilatation, filling with high-density material, and erosion of the sinus wall bone. Patients with AFRS can have a 20% to 90% rate of bone degradation [209]. The initial Bent–Kuhn diagnostic criteria include (1) nasal polyps, (2) stained fungi, (3) eosinophilic mucin, with no fungal invasion of paranasal sinus tissue, (4) type I fungal allergy, and (5) characteristic radiological findings of poor soft tissue density on CT images. Type I hypersensitivity and characteristic CT findings are the only unique factors of the Bentt–Kuhn criteria [210].

Treatment

Surgery is the mainstay of AFRS treatment, which not only can re-establish ventilation and eliminate antigenic stimulation in patients with AFRS but also provide broader access to monitoring, clinical debridement, and the application of topical drugs. Local and systemic corticosteroids are the foundation of AFRS drug treatment. Oral corticosteroids can enhance olfaction and endoscopic scores, reduce polyp formation, and decrease blood eosinophil and IgE level. However, extended use of oral corticosteroids can cause significant side effects. Fortunately, oral corticosteroids cause relatively few adverse events in patients with AFRS [211]. In contrast to oral steroids, topical nasal steroid sprays have a favorable safety profile and can achieve effective drug concentrations in the sinus mucosa without adverse consequences. In addition, topical steroid delivery through novel steroid-eluting sinus implants is also a safe option. Clinical investigations have shown that the use of different steroid-eluting sinus implants can enhance postoperative outcomes of FESS and prevent the recurrence of nasal polyps after sinus surgery [212,213]. An evidence-based review strongly recommends the use of standard topical nasal steroids and nonstandard topical nasal steroid therapy for the treatment of CRS [214]. In addition to standard medical treatment with steroids (systemic/topical), antifungal agents have been applied to decrease the recurrence rate by preventing postoperative fungal development. Several randomized controlled clinical trials of topical/systemic steroids and itraconazole for the treatment of AFRS have recommended itraconazole as a successful substitute to steroids for the postoperative treatment of AFRS [215,216]. In addition, the efficacy of preoperative itraconazole treatment is significantly better than that of postoperative itraconazole, although the recurrence rate before and after surgery was similar [217]. A study to evaluate the efficacy of systemic and local antifungal drugs (alone and in combination) to prevent the recurrence of AFRS after FESS found that local use of fluconazole as a nasal spray and the combination of oral itraconazole and fluconazole considerably reduced the recurrence of AFRS after FESS [218]. Following the treatment of AFRS with antifungal drugs, there was no differences in quality of life, efficacy outcomes, CT scan score, and endoscopy score with the placebo group [219]. Common side effects of antifungal drugs include elevated liver enzymes, congestive heart failure, nausea, rash, headache, malaise, fatigue, and edema. Hence, the use of antifungal drugs is dependent on the overall condition of the patient. Nonetheless, oral antifungal agents are a feasible option for treatment of refractory AFRS, although efficacy, safety, and dosage must be further investigated.

Because AFRS is essentially a type I hypersensitivity reaction, immunotherapy may attenuate the immune response to fungi and reduce the disease burden. Allergen immunotherapy was shown to notably enhance endoscopic mucosal staging, quality of life, and dependence on systemic and oral corticosteroids. Moreover, low-dose subcutaneous fungal immunotherapy targeting fungal allergens could be efficient for the treatment of AFRS. In addition, allergen immunotherapy caused no serious short- or long-term adverse effects in these patients [170,220–223]. Adverse effects and complications did not differ between patients and healthy groups, and fungal immunotherapy was associated with fewer serious adverse effects [224,225]. As part of the treatment plan, allergen immunotherapy that targets fungi should be taken into consideration as it is anticipated to decrease the recurrence of AFRS. Based on this evidence, allergen immunotherapy may be beneficial for patients with AFRS. However, immunotherapy combined with other medical therapies did not reflect the real

impact of immunotherapy on AFRS patients. Therefore, more prospective research is needed to decide the effectiveness of allergen immunotherapy for the treatment of AFRS [226].

4.2.2. Saprophytic Fungal Infestation and Fungal Ball

As compared to AFRS, the incidence is lower for saprophytic fungal infestation and fungal ball. Saprophytic fungal RS has been described as the fungal colonization of nasal secretions or crusted mucosa, which is caused by inhalation exposure of the inflamed or crusted nasal mucosa with fungal spores after surgical intervention. Restricted to superficial crusts/mucosa within the nasal cavity, fungal hyphae does not enter the tissue through epithelial invasion [115,227]. Although there is no typical clinical disease course, there is usually an unpleasant nasal odor. This type of fungal RS is considered to develop into the fungal ball type [228].

Described as a dense collection of fungal hyphae outside the mucosa, a fungal ball histologically exhibits fungal colonization but no invasion and generates minimal mucosal irritation or response [229]. Fungal balls develop slowly and have no specific symptoms. A fungal ball usually involves only a single sinus in the great majority of cases. The maxillary and ethmoid sinuses and the sphenoid sinus are the most often involved sites [230]. The symptoms change based on which sinuses are affected. Common clinical manifestation of maxillary sinus fungal ball includes facial pain, rhinorrhea, nasal obstruction, and nasal odor. Headache and nasal obstruction are common clinical manifestations of ethmoid fungal ball. Sphenoid sinus fungal ball infections are characterized by recurrent retro-orbital pain with visual disturbances [229]. Fungal ball in the sinus occurs mainly in the elderly population, especially women, although the incidence and recurrence rates are low [231]. In addition, invasive fungal RS can develop from non-invasive fungal balls, particularly in older and immunocompromised people [232]. Retrospective analysis shows that most patients are immunocompetent, and about half have dental pulp treatment [198,200]. The pathogenesis of fungal ball in the paranasal sinuses remains unclear. There are two hypotheses about the origin of fungal ball, including sinonasal anatomical variations and dental factors [227]. Anatomical obstruction of the sinus ostium is one example of an anaerobic environment that can promote the growth of fungi [233]. The high frequency of concha bullosa in the fungal ball group of the maxillary sinus may indicate a pathogenic role for this anatomical defect. Because Concha bullosa alters nasal airflow, spore deposition into the maxillary sinus may be facilitated [234]. Some investigations also found a significant difference in the rate of endodontic therapy between patients with fungal ball and those without it [235]. The common species connected with fungal ball include *A. fumigatus*, *A. flavus*, and occasionally *Chrysosporium* and *Penicillium* [198]. The clinical pathological diagnostic criteria for fungal ball in paranasal sinuses are (1) imaging evidence of sinus opacification with or without calcification, (2) a mucoid or clay-like substance with purulence, (3) hyphomycetes (dense aggregates of hyphae separated from the sinus mucosa), (4) non-specific chronic mucosal inflammation with no eosinophil dominance, granulomas, or allergic mucin, and (5) no histological or microscopic evidence of fungal invasion of the mucosa, blood vessels, or bone [236]. Primary treatment of fungal ball includes the removal of fungal components, systemic use of antifungal drugs, and intraoperative and postoperative flushing of the nasal cavity with antibiotic saline.

5. Conclusions

Infectious RS is caused by pathogenic microorganisms and can be triggered by imbalances among the fungi, respiratory viruses, and bacterial species of the microbiome of sinuses (Table 2). With continuous attention to the microbiome in the sinus cavity, microbiota imbalance has been widely considered to be one of the mechanisms of CRS [237]. In addition, mixed infection of multiple pathogenic microorganisms is common in RS [238–240]. Damage to the host immune system or local microecology caused by unbalanced growth of one pathogenic microorganism renders the host more susceptible to infection by other pathogenic microorganisms. Therefore, it is necessary to focus on the occurrence of infectious RS after infection with other pathogenic microorganism, early diagnosis, and early treatment.

Table 2. Comparisons of RS caused by viruses, bacteria, and fungi.

	Clinical Characteristics	Common Types of Pathogens	Pathogenesis and Host Immune Response	Diagnosis	Treatment	Reference
Viral RS	Mostly acute and usually lasts less than 10 days. Common cold symptoms, a blocked nose or a feeling of congestion, nasal discharge, green/yellow colored mucus or even pus, or facial pain or pressure, headache, and reduction/loss of smell.	Coronavirus, adenovirus, human rhinovirus, influenza virus, and respiratory syncytial virus.	Binding to the sinonasal epithelium through specific receptors, then entering cells and replicating. Triggering intrinsic immune response dominated by IFN and type 2 inflammatory response.	The clinical manifestations of sinus inflammation, sinus CT, and molecular detection technology.	Antiviral drug treatment and surgery.	[1,8,9,11–14,35,36,38–41,52–55,57,58,60–71]
Bacterial RS	Patients feel more unwell than a typical cold and may result in severe facial pain located around one side, a high fever (>38°), mucus that looks green, yellow, or rusty brown. Severe patients usually present with symptoms such as nasal blockage/congestion, nasal discharge, altered sense of smell, and facial pain.	*S. aureus*, *S. pneumoniae*, *M. catarrhalis*, *P. aeruginosa*	Bacterial components and virulence factors. Regulates innate and adaptive immunity by disrupting tissue barrier function, promoting impaired mucociliary clearance, driving polyps, and promoting type 2 inflammation.	Microbial culture, patient's clinical symptoms, and sinus CT.	Steroids, antibiotics, nasal saline irrigation, surgery, immunoglobulin replacement.	[1,2,72–107]
Fungal RS	The most common clinical manifestations were ocular swelling, exophthalmos, and headache.	Typical *Mucor*, *Aspergillus*, and atypical fungi (*Alternaria*, *Candida*, *Fusarium*, *Paecilomyces*, *Scedosporium* and *Scopularopsis*.)	AFRS: epithelial activation with concomitant EC apoptosis and loss of EB integrity, an excessive type 2 immune response characterized by cytokines, such as IL-4, IL-5, and IL-13, and an upregulation of adaptive immune responses characterized by elevated IgE levels.	In addition to the above mentioned, fungal RS can be diagnosed through special staining techniques such as periodic acid Schiff staining.	Early surgical debridement, antifungal therapy, and reversal of underlying immunodeficiency.	[109,121–123,137–144,146,173,182,183,186,187,189,193–207,219–235]

Pathogens disrupt the EB of the nasal mucosa and activate the immune response, which is considered an important mechanism in the pathogenesis of RS. These immune responses not only recruit neutrophils and macrophages to activate the innate immune response but also stimulate the release of IL-13, IL-5, IL-4, and IL-9, thereby promoting type 2 inflammation. The infiltration of various immune cells and the increased production of an array of inflammatory mediators ultimately leads to tissue edema and mucus generation. Meanwhile, damage to the EB increases the risk of pathogen invasion. In addition, recent investigations have confirmed the increased production of IL-17A in CRS patients. The overexpression of IL-17A promotes CRS through tissue remodeling, eosinophilic accumulation, and neutrophilic infiltration. Although significant progress has been made to elucidate the pathogenesis of infectious RS, unique biomarkers and evidence-based treatment options are still lacking for infectious RS; thus, further investigations are warranted.

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References

1. 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]
2. Fokkens, W.J.; Lund, V.J.; Mullol, J.; Bachert, C.; Alobid, I.; Baroody, F.; Cohen, N.; Cervin, A.; Douglas, R.; Gevaert, P.; et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* **2012**, *50*, 1–12. [CrossRef] [PubMed]
3. Martis, N.; Chirio, D.; Queyrel-Moranne, V.; Zenut, M.C.; Rocher, F.; Fuzibet, J.G. Tocilizumab-induced hypofibrinogenemia: A report of 7 cases. *Jt. Bone Spine* **2017**, *84*, 369–370. [CrossRef] [PubMed]
4. Rosenfeld, R.M.; Piccirillo, J.F.; Chandrasekhar, S.S.; Brook, I.; Ashok Kumar, K.; Kramper, M.; Orlandi, R.R.; Palmer, J.N.; Patel, Z.M.; Peters, A.; et al. Clinical practice guideline (update): Adult sinusitis. *Otolaryngol. Head Neck Surg.* **2015**, *152*, S1–S39. [CrossRef]
5. Smith, S.S.; Evans, C.T.; Tan, B.K.; Chandra, R.K.; Smith, S.B.; Kern, R.C. National burden of antibiotic use for adult rhinosinusitis. *J. Allergy Clin. Immunol.* **2013**, *132*, 1230–1232. [CrossRef] [PubMed]
6. Smith, S.S.; Kern, R.C.; Chandra, R.K.; Tan, B.K.; Evans, C.T. Variations in antibiotic prescribing of acute rhinosinusitis in United States ambulatory settings. *Otolaryngol. Head Neck Surg.* **2013**, *148*, 852–859. [CrossRef]
7. Lee, L.N.; Bhattacharyya, N. Regional and specialty variations in the treatment of chronic rhinosinusitis. *Laryngoscope* **2011**, *121*, 1092–1097. [CrossRef] [PubMed]
8. Cho, G.S.; Moon, B.J.; Lee, B.J.; Gong, C.H.; Kim, N.H.; Kim, Y.S.; Kim, H.S.; Jang, Y.J. High rates of detection of respiratory viruses in the nasal washes and mucosae of patients with chronic rhinosinusitis. *J. Clin. Microbiol.* **2013**, *51*, 979–984. [CrossRef]
9. Liao, B.; Hu, C.Y.; Liu, T.; Liu, Z. Respiratory viral infection in the chronic persistent phase of chronic rhinosinusitis. *Laryngoscope* **2014**, *124*, 832–837. [CrossRef]
10. Wood, A.J.; Antoszewska, H.; Fraser, J.; Douglas, R.G. Is chronic rhinosinusitis caused by persistent respiratory virus infection? *Int. Forum Allergy Rhinol.* **2011**, *1*, 95–100. [CrossRef]
11. Rowan, N.R.; Lee, S.; Sahu, N.; Kanaan, A.; Cox, S.; Phillips, C.D.; Wang, E.W. The role of viruses in the clinical presentation of chronic rhinosinusitis. *Am. J. Rhinol. Allergy* **2015**, *29*, e197–e200. [CrossRef]
12. Volpe, S.; Irish, J.; Palumbo, S.; Lee, E.; Herbert, J.; Ramadan, I.; Chang, E.H. Viral infections and chronic rhinosinusitis. *J. Allergy Clin. Immunol.* **2023**, *152*, 819–826. [CrossRef]
13. Basharat, U.; Aiche, M.M.; Kim, M.M.; Sohal, M.; Chang, E.H. Are rhinoviruses implicated in the pathogenesis of sinusitis and chronic rhinosinusitis exacerbations? A comprehensive review. *Int. Forum Allergy Rhinol.* **2019**, *9*, 1159–1188. [CrossRef]
14. Nakagome, K.; Bochkov, Y.A.; Ashraf, S.; Brockman-Schneider, R.A.; Evans, M.D.; Pasic, T.R.; Gern, J.E. Effects of rhinovirus species on viral replication and cytokine production. *J. Allergy Clin. Immunol.* **2014**, *134*, 332–341. [CrossRef] [PubMed]
15. Essaidi-Laziosi, M.; Brito, F.; Benaoudia, S.; Royston, L.; Cagno, V.; Fernandes-Rocha, M.; Piuz, I.; Zdobnov, E.; Huang, S.; Constant, S.; et al. Propagation of respiratory viruses in human airway epithelia reveals persistent virus-specific signatures. *J. Allergy Clin. Immunol.* **2018**, *141*, 2074–2084. [CrossRef]

16. Kloepfer, K.M.; Sarsani, V.K.; Poroyko, V.; Lee, W.M.; Pappas, T.E.; Kang, T.; Grindle, K.A.; Bochkov, Y.A.; Janga, S.C.; Lemanske, R.F., Jr.; et al. Community-acquired rhinovirus infection is associated with changes in the airway microbiome. *J. Allergy Clin. Immunol.* **2017**, *140*, 312–315.e318. [CrossRef] [PubMed]
17. Bochkov, Y.A.; Gern, J.E. Rhinoviruses and their receptors: Implications for allergic disease. *Curr. Allergy Asthma Rep.* **2016**, *16*, 30. [CrossRef]
18. Choi, H.; Fleming, N.W.; Serikov, V.B. Contact activation via ICAM-1 induces changes in airway epithelial permeability in vitro. *Immunol. Investig.* **2007**, *36*, 59–72. [CrossRef] [PubMed]
19. Wiesolek, H.L.; Bui, T.M.; Lee, J.J.; Dalal, P.; Finkielsztein, A.; Batra, A.; Thorp, E.B.; Sumagin, R. Intercellular adhesion molecule 1 functions as an efferocytosis receptor in inflammatory macrophages. *Am. J. Pathol.* **2020**, *190*, 874–885. [CrossRef]
20. Griggs, T.F.; Bochkov, Y.A.; Basnet, S.; Pasic, T.R.; Brockman-Schneider, R.A.; Palmenberg, A.C.; Gern, J.E. Rhinovirus C targets ciliated airway epithelial cells. *Respir. Res.* **2017**, *18*, 84. [CrossRef]
21. Basnet, S.; Bochkov, Y.A.; Brockman-Schneider, R.A.; Kuipers, I.; Aesif, S.W.; Jackson, D.J.; Lemanske, R.F., Jr.; Ober, C.; Palmenberg, A.C.; Gern, J.E. CDHR3 asthma-risk genotype affects susceptibility of airway epithelium to rhinovirus c infections. *Am. J. Respir. Cell Mol. Biol.* **2019**, *61*, 450–458. [CrossRef]
22. Chang, E.H.; Willis, A.L.; McCrary, H.C.; Noutsios, G.T.; Le, C.H.; Chiu, A.G.; Mansfield, C.J.; Reed, D.R.; Brooks, S.G.; Adappa, N.D.; et al. Association between the CDHR3 rs6967330 risk allele and chronic rhinosinusitis. *J. Allergy Clin. Immunol.* **2017**, *139*, 1990–1992.e1992. [CrossRef]
23. Chirkova, T.; Lin, S.; Oomens, A.G.P.; Gaston, K.A.; Boyoglu-Barnum, S.; Meng, J.; Stobart, C.C.; Cotton, C.U.; Hartert, T.V.; Moore, M.L.; et al. CX3CR1 is an important surface molecule for respiratory syncytial virus infection in human airway epithelial cells. *J. Gen. Virol.* **2015**, *96*, 2543–2556. [CrossRef] [PubMed]
24. Feng, Z.; Xu, L.; Xie, Z. Receptors for respiratory syncytial virus infection and host factors regulating the life cycle of respiratory syncytial virus. *Front. Cell Infect. Microbiol.* **2022**, *12*, 858629. [CrossRef] [PubMed]
25. García-Sastre, A. Influenza virus receptor specificity: Disease and transmission. *Am. J. Pathol.* **2010**, *176*, 1584–1585. [CrossRef]
26. Yeager, C.L.; Ashmun, R.A.; Williams, R.K.; Cardellichio, C.B.; Shapiro, L.H.; Look, A.T.; Holmes, K.V. Human aminopeptidase N is a receptor for human coronavirus 229E. *Nature* **1992**, *357*, 420–422. [CrossRef]
27. Sungnak, W.; Huang, N.; Bécavin, C.; Berg, M.; Queen, R.; Litvinukova, M.; Talavera-López, C.; Maatz, H.; Reichart, D.; Sampaziotis, F.; et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat. Med.* **2020**, *26*, 681–687. [CrossRef]
28. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 cell entry depends on ace2 and tmprss2 and is blocked by a clinically proven protease inhibitor. *Cell* **2020**, *181*, 271–280.e278. [CrossRef]
29. Liu, Z.; Xiao, X.; Wei, X.; Li, J.; Yang, J.; Tan, H.; Zhu, J.; Zhang, Q.; Wu, J.; Liu, L. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. *J. Med. Virol.* **2020**, *92*, 595–601. [CrossRef] [PubMed]
30. Chen, L.; Hao, G. The role of angiotensin-converting enzyme 2 in coronaviruses/influenza viruses and cardiovascular disease. *Cardiovasc. Res.* **2020**, *116*, 1932–1936. [CrossRef]
31. Chang, E.H.; Willis, A.L.; Romanoski, C.E.; Cusanovich, D.A.; Pouladi, N.; Li, J.; Lussier, Y.A.; Martinez, F.D. Rhinovirus infections in individuals with asthma increase ACE2 expression and cytokine pathways implicated in COVID-19. *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 753–755. [CrossRef] [PubMed]
32. Lee, S.W.; Kim, S.Y.; Moon, S.Y.; Yang, J.M.; Ha, E.K.; Jee, H.M.; Shin, J.I.; Cho, S.H.; Yon, D.K.; Suh, D.I. Estimating COVID-19 infection and severity risks in patients with chronic rhinosinusitis: A korean nationwide cohort study. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 2262–2271.e2262. [CrossRef] [PubMed]
33. Wang, M.; Bu, X.; Fang, G.; Luan, G.; Huang, Y.; Akdis, C.A.; Wang, C.; Zhang, L. Distinct expression of SARS-CoV-2 receptor ACE2 correlates with endotypes of chronic rhinosinusitis with nasal polyps. *Allergy* **2021**, *76*, 789–803. [CrossRef]
34. Huang, W.Q.; Huang, Z.Z.; Lai, X.P.; Li, Y.; Chen, X.H.; Wu, H.T.; Chang, L.H.; Zhang, Y.N.; Zhang, G.H. The expression profile and potential regulatory mechanism of ACE2 in chronic rhinosinusitis with nasal polyps. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* **2022**, *57*, 692–698.
35. Kuek, L.E.; Lee, R.J. First contact: The role of respiratory cilia in host-pathogen interactions in the airways. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2020**, *319*, L603–L619. [CrossRef]
36. Robinot, R.; Hubert, M.; de Melo, G.D.; Lazarini, F.; Bruel, T.; Smith, N.; Levallois, S.; Larrous, F.; Fernandes, J.; Gellenoncourt, S.; et al. SARS-CoV-2 infection induces the dedifferentiation of multiciliated cells and impairs mucociliary clearance. *Nat. Commun.* **2021**, *12*, 4354. [CrossRef] [PubMed]
37. Nicolas de Lamballerie, C.; Pizzorno, A.; Dubois, J.; Julien, T.; Padey, B.; Bouveret, M.; Traversier, A.; Legras-Lachuer, C.; Lina, B.; Boivin, G.; et al. Characterization of cellular transcriptomic signatures induced by different respiratory viruses in human reconstituted airway epithelia. *Sci. Rep.* **2019**, *9*, 11493. [CrossRef]
38. Wu, N.H.; Yang, W.; Beineke, A.; Dijkman, R.; Matrosovich, M.; Baumgärtner, W.; Thiel, V.; Valentin-Weigand, P.; Meng, F.; Herrler, G. The differentiated airway epithelium infected by influenza viruses maintains the barrier function despite a dramatic loss of ciliated cells. *Sci. Rep.* **2016**, *6*, 39668. [CrossRef]

39. Smith, C.M.; Kulkarni, H.; Radhakrishnan, P.; Rutman, A.; Bankart, M.J.; Williams, G.; Hirst, R.A.; Easton, A.J.; Andrew, P.W.; O'Callaghan, C. Ciliary dyskinesia is an early feature of respiratory syncytial virus infection. *Eur. Respir. J.* **2014**, *43*, 485–496. [CrossRef]
40. Du, X.; Yang, Y.; Xiao, G.; Yang, M.; Yuan, L.; Qin, L.; He, R.; Wang, L.; Wu, M.; Wu, S.; et al. Respiratory syncytial virus infection-induced mucus secretion by down-regulation of miR-34b/c-5p expression in airway epithelial cells. *J. Cell Mol. Med.* **2020**, *24*, 12694–12705. [CrossRef]
41. Yeo, N.K.; Jang, Y.J. Rhinovirus infection-induced alteration of tight junction and adherens junction components in human nasal epithelial cells. *Laryngoscope* **2010**, *120*, 346–352. [CrossRef] [PubMed]
42. Smallcombe, C.C.; Linfield, D.T.; Harford, T.J.; Bokun, V.; Ivanov, A.I.; Piedimonte, G.; Rezaee, F. Disruption of the airway epithelial barrier in a murine model of respiratory syncytial virus infection. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2019**, *316*, L358–L368. [CrossRef] [PubMed]
43. Pharo, E.A.; Williams, S.M.; Boyd, V.; Sundaramoorthy, V.; Durr, P.A.; Baker, M.L. Host-pathogen responses to pandemic influenza h1n1pdm09 in a human respiratory airway model. *Viruses* **2020**, *12*, 679. [CrossRef] [PubMed]
44. Chang, E.H.; Stern, D.A.; Willis, A.L.; Guerra, S.; Wright, A.L.; Martinez, F.D. Early life risk factors for chronic sinusitis: A longitudinal birth cohort study. *J. Allergy Clin. Immunol.* **2018**, *141*, 1291–1297.e1292. [CrossRef] [PubMed]
45. Jiao, J.; Wang, C.; Zhang, L. Epithelial physical barrier defects in chronic rhinosinusitis. *Expert. Rev. Clin. Immunol.* **2019**, *15*, 679–688. [CrossRef] [PubMed]
46. Stevens, W.W.; Schleimer, R.P.; Kern, R.C. Chronic rhinosinusitis with nasal polyps. *J. Allergy Clin. Immunol. Pract.* **2016**, *4*, 565–572. [CrossRef] [PubMed]
47. Eloy, P.; Poirrier, A.L.; De Dorlodot, C.; Van Zele, T.; Watelet, J.B.; Bertrand, B. Actual concepts in rhinosinusitis: A review of clinical presentations, inflammatory pathways, cytokine profiles, remodeling, and management. *Curr. Allergy Asthma Rep.* **2011**, *11*, 146–162. [CrossRef] [PubMed]
48. García-Sastre, A.; Biron, C.A. Type 1 interferons and the virus-host relationship: A lesson in détente. *Science* **2006**, *312*, 879–882. [CrossRef] [PubMed]
49. Kawai, T.; Akira, S. Innate immune recognition of viral infection. *Nat. Immunol.* **2006**, *7*, 131–137. [CrossRef]
50. Katze, M.G.; He, Y.; Gale, M., Jr. Viruses and interferon: A fight for supremacy. *Nat. Rev. Immunol.* **2002**, *2*, 675–687. [CrossRef]
51. Makris, S.; Paulsen, M.; Johansson, C. Type I interferons as regulators of lung inflammation. *Front. Immunol.* **2017**, *8*, 259. [CrossRef]
52. Tan, K.S.; Ong, H.H.; Yan, Y.; Liu, J.; Li, C.; Ong, Y.K.; Thong, K.T.; Choi, H.W.; Wang, D.Y.; Chow, V.T. In vitro model of fully differentiated human nasal epithelial cells infected with rhinovirus reveals epithelium-initiated immune responses. *J. Infect. Dis.* **2018**, *217*, 906–915. [CrossRef] [PubMed]
53. Kim, J.H.; Kim, Y.S.; Cho, G.S.; Kim, N.H.; Gong, C.H.; Lee, B.J.; Jang, Y.J. Human rhinovirus-induced proinflammatory cytokine and interferon-β responses in nasal epithelial cells from chronic rhinosinusitis patients. *Allergy Asthma Immunol. Res.* **2015**, *7*, 489–496. [CrossRef]
54. Lee, S.H.; Han, M.S.; Lee, T.H.; Lee, D.B.; Park, J.H.; Lee, S.H.; Kim, T.H. Rhinovirus-induced anti-viral interferon secretion is not deficient and not delayed in sinonasal epithelial cells of patients with chronic rhinosinusitis with nasal polyp. *Front. Immunol.* **2022**, *13*, 1025796. [CrossRef]
55. Hwang, J.W.; Lee, K.J.; Choi, I.H.; Han, H.M.; Kim, T.H.; Lee, S.H. Decreased expression of type I (IFN-β) and type III (IFN-λ) interferons and interferon-stimulated genes in patients with chronic rhinosinusitis with and without nasal polyps. *J. Allergy Clin. Immunol.* **2019**, *144*, 1551–1565.e1552. [CrossRef]
56. Altman, M.C.; Gill, M.A.; Whalen, E.; Babineau, D.C.; Shao, B.; Liu, A.H.; Jepson, B.; Gruchalla, R.S.; O'Connor, G.T.; Pongracic, J.A.; et al. Transcriptome networks identify mechanisms of viral and nonviral asthma exacerbations in children. *Nat. Immunol.* **2019**, *20*, 637–651. [CrossRef]
57. Jackson, D.J.; Makrinioti, H.; Rana, B.M.; Shamji, B.W.; Trujillo-Torralbo, M.B.; Footitt, J.; Jerico, D.-R.; Telcian, A.G.; Nikonova, A.; Zhu, J.; et al. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. *Am. J. Respir. Crit. Care Med.* **2014**, *190*, 1373–1382. [CrossRef] [PubMed]
58. Agac, A.; Kolbe, S.M.; Ludlow, M.; Osterhaus, A.; Meineke, R.; Rimmelzwaan, G.F. Host responses to respiratory syncytial virus infection. *Viruses* **2023**, *15*, 1999. [CrossRef]
59. Hijano, D.R.; Vu, L.D.; Kauvar, L.M.; Tripp, R.A.; Polack, F.P.; Cormier, S.A. Role of type I interferon (IFN) in the respiratory syncytial virus (RSV) immune response and disease severity. *Front. Immunol.* **2019**, *10*, 566. [CrossRef] [PubMed]
60. Zhang, N.; Wang, L.; Deng, X.; Liang, R.; Su, M.; He, C.; Hu, L.; Su, Y.; Ren, J.; Yu, F.; et al. Recent advances in the detection of respiratory virus infection in humans. *J. Med. Virol.* **2020**, *92*, 408–417. [CrossRef]
61. McAdam, A.J.; Riley, A.M. Developments in tissue culture detection of respiratory viruses. *Clin. Lab. Med.* **2009**, *29*, 623–634. [CrossRef] [PubMed]
62. Dunn, J.J.; Ginocchio, C.C. Can newly developed, rapid immunochromatographic antigen detection tests be reliably used for the laboratory diagnosis of influenza virus infections? *J. Clin. Microbiol.* **2015**, *53*, 1790–1796. [CrossRef]
63. Selvarangan, R.; Abel, D.; Hamilton, M. Comparison of BD Directigen EZ RSV and Binax NOW RSV tests for rapid detection of respiratory syncytial virus from nasopharyngeal aspirates in a pediatric population. *Diagn. Microbiol. Infect. Dis.* **2008**, *62*, 157–161. [CrossRef]

64. Zaky, S.; Kamel, S.E.; Hassan, M.S.; Sallam, N.A.; Shahata, M.A.; Helal, S.R.; Mahmoud, H. Preliminary results of ozone therapy as a possible treatment for patients with chronic hepatitis C. *J. Altern. Complement Med.* **2011**, *17*, 259–263. [CrossRef]
65. Rowen, R.J. Ozone and oxidation therapies as a solution to the emerging crisis in infectious disease management: A review of current knowledge and experience. *Med. Gas. Res.* **2019**, *9*, 232–237. [CrossRef] [PubMed]
66. Ankcorn, M.; Gallacher, J.; Ijaz, S.; Taha, Y.; Harvala, H.; Maclennan, S.; Thomson, E.C.; Davis, C.; Singer, J.B.; da Silva Filipe, A.; et al. Convalescent plasma therapy for persistent hepatitis E virus infection. *J. Hepatol.* **2019**, *71*, 434–438. [CrossRef] [PubMed]
67. van Griensven, J.; Edwards, T.; de Lamballerie, X.; Semple, M.G.; Gallian, P.; Baize, S.; Horby, P.W.; Raoul, H.; Magassouba, N.; Antierens, A.; et al. Evaluation of convalescent plasma for ebola virus disease in guinea. *N. Engl. J. Med.* **2016**, *374*, 33–42. [CrossRef]
68. Duan, K.; Liu, B.; Li, C.; Zhang, H.; Yu, T.; Qu, J.; Zhou, M.; Chen, L.; Meng, S.; Hu, Y.; et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 9490–9496. [CrossRef] [PubMed]
69. Shen, C.; Wang, Z.; Zhao, F.; Yang, Y.; Li, J.; Yuan, J.; Wang, F.; Li, D.; Yang, M.; Xing, L.; et al. Treatment of 5 critically Ill patients with COVID-19 with convalescent plasma. *JAMA* **2020**, *323*, 1582–1589. [CrossRef]
70. Coleman, C.M.; Liu, Y.V.; Mu, H.; Taylor, J.K.; Massare, M.; Flyer, D.C.; Smith, G.E.; Frieman, M.B. Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice. *Vaccine* **2014**, *32*, 3169–3174. [CrossRef]
71. El Kantar, S.; Nehmeh, B.; Saad, P.; Mitri, G.; Estephan, C.; Mroueh, M.; Akoury, E.; Taleb, R.I. Derivatization and combination therapy of current COVID-19 therapeutic agents: A review of mechanistic pathways, adverse effects, and binding sites. *Drug Discov. Today* **2020**, *25*, 1822–1838. [CrossRef] [PubMed]
72. Brook, I. Microbiology and antimicrobial management of sinusitis. *J. Laryngol. Otol.* **2005**, *119*, 251–258. [CrossRef] [PubMed]
73. Martens, K.; Seys, S.F.; Alpizar, Y.A.; Schrijvers, R.; Bullens, D.M.A.; Breynaert, C.; Lebeer, S.; Steelant, B. Staphylococcus aureus enterotoxin B disrupts nasal epithelial barrier integrity. *Clin. Exp. Allergy* **2021**, *51*, 87–98. [CrossRef]
74. Shaghayegh, G.; Cooksley, C.; Ramezanpour, M.; Wormald, P.J.; Psaltis, A.J.; Vreugde, S. Chronic rhinosinusitis, *S. aureus* biofilm and secreted products, inflammatory responses, and disease severity. *Biomedicines* **2022**, *10*, 1362. [CrossRef]
75. Hayes, S.M.; Biggs, T.C.; Goldie, S.P.; Harries, P.G.; Walls, A.F.; Allan, R.N.; Pender, S.L.F.; Salib, R.J. *Staphylococcus aureus* internalization in mast cells in nasal polyps: Characterization of interactions and potential mechanisms. *J. Allergy Clin. Immunol.* **2020**, *145*, 147–159. [CrossRef] [PubMed]
76. Teufelberger, A.R.; Bröker, B.M.; Krysko, D.V.; Bachert, C.; Krysko, O. *Staphylococcus aureus* orchestrates type 2 airway diseases. *Trends Mol. Med.* **2019**, *25*, 696–707. [CrossRef]
77. Yoon, Y.H.; Yeon, S.H.; Choi, M.R.; Jang, Y.S.; Kim, J.A.; Oh, H.W.; Jun, X.; Park, S.K.; Heo, J.Y.; Rha, K.S.; et al. Altered mitochondrial functions and morphologies in epithelial cells are associated with pathogenesis of chronic rhinosinusitis with nasal polyps. *Allergy Asthma Immunol. Res.* **2020**, *12*, 653–668. [CrossRef]
78. Murphy, J.; Ramezanpour, M.; Stach, N.; Dubin, G.; Psaltis, A.J.; Wormald, P.J.; Vreugde, S. *Staphylococcus aureus* V8 protease disrupts the integrity of the airway epithelial barrier and impairs IL-6 production in vitro. *Laryngoscope* **2018**, *128*, E8–E15. [CrossRef]
79. Chegini, Z.; Noei, M.; Hemmati, J.; Arabestani, M.R.; Shariati, A. The destruction of mucosal barriers, epithelial remodeling, and impaired mucociliary clearance: Possible pathogenic mechanisms of *Pseudomonas aeruginosa* and *Staphylococcus aureus* in chronic rhinosinusitis. *Cell Commun. Signal* **2023**, *21*, 306. [CrossRef]
80. Tuli, J.F.; Ramezanpour, M.; Cooksley, C.; Psaltis, A.J.; Wormald, P.J.; Vreugde, S. Association between mucosal barrier disruption by *Pseudomonas aeruginosa* exoproteins and asthma in patients with chronic rhinosinusitis. *Allergy* **2021**, *76*, 3459–3469. [CrossRef]
81. Li, J.; Ramezanpour, M.; Fong, S.A.; Cooksley, C.; Murphy, J.; Suzuki, M.; Psaltis, A.J.; Wormald, P.J.; Vreugde, S. *Pseudomonas aeruginosa* exoprotein-induced barrier disruption correlates with elastase activity and marks chronic rhinosinusitis severity. *Front. Cell Infect. Microbiol.* **2019**, *9*, 38. [CrossRef] [PubMed]
82. Nomura, K.; Obata, K.; Keira, T.; Miyata, R.; Hirakawa, S.; Takano, K.; Kohno, T.; Sawada, N.; Himi, T.; Kojima, T. *Pseudomonas aeruginosa* elastase causes transient disruption of tight junctions and downregulation of PAR-2 in human nasal epithelial cells. *Respir. Res.* **2014**, *15*, 21. [CrossRef] [PubMed]
83. Galli, J.; Calò, L.; Ardito, F.; Imperiali, M.; Bassotti, E.; Passali, G.C.; La Torre, G.; Paludetti, G.; Fadda, G. Damage to ciliated epithelium in chronic rhinosinusitis: What is the role of bacterial biofilms? *Ann. Otol. Rhinol. Laryngol.* **2008**, *117*, 902–908. [CrossRef] [PubMed]
84. Huang, Y.; Qin, F.; Li, S.; Yin, J.; Hu, L.; Zheng, S.; He, L.; Xia, H.; Liu, J.; Hu, W. The mechanisms of biofilm antibiotic resistance in chronic rhinosinusitis: A review. *Medicine* **2022**, *101*, e32168. [CrossRef] [PubMed]
85. Głowacki, R.; Tomaszewski, K.A.; Stręk, P.; Tomaszewska, I.M.; Zgórska-Świerzy, K.; Markiewicz, B.; Składzień, J. The influence of bacterial biofilm on the clinical outcome of chronic rhinosinusitis: A prospective, double-blind, scanning electron microscopy study. *Eur. Arch. Otorhinolaryngol.* **2014**, *271*, 1015–1021. [CrossRef] [PubMed]
86. Hoggard, M.; Wagner Mackenzie, B.; Jain, R.; Taylor, M.W.; Biswas, K.; Douglas, R.G. Chronic rhinosinusitis and the evolving understanding of microbial ecology in chronic inflammatory mucosal disease. *Clin. Microbiol. Rev.* **2017**, *30*, 321–348. [CrossRef] [PubMed]
87. Kaliniak, S.; Fiedoruk, K.; Spałek, J.; Piktel, E.; Durnaś, B.; Góźdź, S.; Bucki, R.; Okła, S. Remodeling of paranasal sinuses mucosa functions in response to biofilm-induced inflammation. *J. Inflamm. Res.* **2024**, *17*, 1295–1323. [CrossRef] [PubMed]

88. Popov, G.; Aleksandrov, R.; Petkova, V.; Kaneva, R.; Gergova, R.; Kundurzhiev, T.; Popova, D. Analysis of bacterial biofilm formation and MUC5AC and MUC5B expression in chronic rhinosinusitis patients. *J. Clin. Med.* **2023**, *12*, 1808. [CrossRef] [PubMed]
89. Mladina, R.; Skitarelić, N.; Musić, S.; Ristić, M. A biofilm exists on healthy mucosa of the paranasal sinuses: A prospectively performed, blinded, scanning electron microscope study. *Clin. Otolaryngol.* **2010**, *35*, 104–110. [CrossRef]
90. Zhang, Z.; Adappa, N.D.; Chiu, A.G.; Doghramji, L.J.; Cohen, N.A.; Palmer, J.N. Biofilm-forming bacteria and quality of life improvement after sinus surgery. *Int. Forum Allergy Rhinol.* **2015**, *5*, 643–649. [CrossRef]
91. Shaghayegh, G.; Cooksley, C.; Bouras, G.; Nepal, R.; Houtak, G.; Panchatcharam, B.S.; Fenix, K.A.; Psaltis, A.J.; Wormald, P.J.; Vreugde, S. *Staphylococcus aureus* biofilm properties and chronic rhinosinusitis severity scores correlate positively with total CD4+ T-cell frequencies and inversely with its Th1, Th17 and regulatory cell frequencies. *Immunology* **2023**, *170*, 120–133. [CrossRef] [PubMed]
92. Panchatcharam, B.S.; Cooksley, C.M.; Ramezanpour, M.; Vediappan, R.S.; Bassiouni, A.; Wormald, P.J.; Psaltis, A.J.; Vreugde, S. *Staphylococcus aureus* biofilm exoproteins are cytotoxic to human nasal epithelial barrier in chronic rhinosinusitis. *Int. Forum Allergy Rhinol.* **2020**, *10*, 871–883. [CrossRef] [PubMed]
93. Foreman, A.; Holtappels, G.; Psaltis, A.J.; Jervis-Bardy, J.; Field, J.; Wormald, P.J.; Bachert, C. Adaptive immune responses in *Staphylococcus aureus* biofilm-associated chronic rhinosinusitis. *Allergy* **2011**, *66*, 1449–1456. [CrossRef] [PubMed]
94. Martinez, F.O.; Helming, L.; Gordon, S. Alternative activation of macrophages: An immunologic functional perspective. *Annu. Rev. Immunol.* **2009**, *27*, 451–483. [CrossRef] [PubMed]
95. Tyler, M.A.; Lam, K.; Marino, M.J.; Yao, W.C.; Schmale, I.; Citardi, M.J.; Luong, A.U. Revisiting the controversy: The role of fungi in chronic rhinosinusitis. *Int. Forum Allergy Rhinol.* **2021**, *11*, 1577–1587. [CrossRef] [PubMed]
96. Vickery, T.W.; Ramakrishnan, V.R.; Suh, J.D. The role of *Staphylococcus aureus* in patients with chronic sinusitis and nasal polyposis. *Curr. Allergy Asthma Rep.* **2019**, *19*, 21. [CrossRef] [PubMed]
97. Zawadzka-Głos, L. Microbiota and antibiotic therapy in rhinosinusitis. *Otolaryngol. Pol.* **2023**, *77*, 36–42. [CrossRef] [PubMed]
98. Tuli, J.F.; Ramezanpour, M.; Cooksley, C.; Bouras, G.S.; Ogi, K.; Feizi, S.; Nepal, R.; Psaltis, A.J.; Wormald, P.J.; Vreugde, S. Increased antibiotic resistance of *Pseudomonas aeruginosa* isolates from chronic rhinosinusitis patients grown in anaerobic conditions. *Laryngoscope Investig. Otolaryngol.* **2024**, *9*, e1244. [CrossRef]
99. Bendouah, Z.; Barbeau, J.; Hamad, W.A.; Desrosiers, M. Use of an in vitro assay for determination of biofilm-forming capacity of bacteria in chronic rhinosinusitis. *Am. J. Rhinol.* **2006**, *20*, 434–438. [CrossRef]
100. Paramasivan, S.; Drilling, A.J.; Jardeleza, C.; Jervis-Bardy, J.; Vreugde, S.; Wormald, P.J. Methylglyoxal-augmented manuka honey as a topical anti-*Staphylococcus aureus* biofilm agent: Safety and efficacy in an in vivo model. *Int. Forum Allergy Rhinol.* **2014**, *4*, 187–195. [CrossRef]
101. Schürmann, M.; Oppel, F.; Gottschalk, M.; Büker, B.; Jantos, C.A.; Knabbe, C.; Hütten, A.; Kaltschmidt, B.; Kaltschmidt, C.; Sudhoff, H. The therapeutic effect of 1,8-cineol on pathogenic bacteria species present in chronic rhinosinusitis. *Front. Microbiol.* **2019**, *10*, 2325. [CrossRef] [PubMed]
102. Jain, R.; Lee, T.; Hardcastle, T.; Biswas, K.; Radcliff, F.; Douglas, R. The in vitro effect of xylitol on chronic rhinosinusitis biofilms. *Rhinology* **2016**, *54*, 323–328. [CrossRef] [PubMed]
103. Sharahi, J.Y.; Azimi, T.; Shariati, A.; Safari, H.; Tehrani, M.K.; Hashemi, A. Advanced strategies for combating bacterial biofilms. *J. Cell Physiol.* **2019**, *234*, 14689–14708. [CrossRef] [PubMed]
104. Abuzeid, W.M.; Girish, V.M.; Fastenberg, J.H.; Draganski, A.R.; Lee, A.Y.; Nosanchuk, J.D.; Friedman, J.M. Nitric oxide-releasing microparticles as a potent antimicrobial therapeutic against chronic rhinosinusitis bacterial isolates. *Int. Forum Allergy Rhinol.* **2018**, *8*, 1190–1198. [CrossRef] [PubMed]
105. Jardeleza, C.; Thierry, B.; Rao, S.; Rajiv, S.; Drilling, A.; Miljkovic, D.; Paramasivan, S.; James, C.; Dong, D.; Thomas, N.; et al. An in vivo safety and efficacy demonstration of a topical liposomal nitric oxide donor treatment for *Staphylococcus aureus* biofilm-associated rhinosinusitis. *Transl. Res.* **2015**, *166*, 683–692. [CrossRef]
106. Krivopalov, A.A.; Moroz, N.V.; Belicheva, E.G.; Lengina, M.A. Phage therapy in overcoming antibiotic resistance in chronic rhinosinusitis. *Vestn. Otorinolaringol.* **2023**, *88*, 48–55. [CrossRef]
107. Garvey, E.A.; Arielle Best, K.; Naimi, B.; Duffy, A.; Hannikainen, P.; Kahn, C.; Farquhar, D.; Rosen, M.; Rabinowitz, M.; Fung, S.; et al. Benefits of immunoglobulin (Ig) replacement therapy for primary and secondary immunodeficiency in chronic rhinosinusitis. *Otolaryngol. Head Neck Surg.* **2024**, *170*, 968–971. [CrossRef]
108. Alford, M.A.; Choi, K.G.; Trimble, M.J.; Masoudi, H.; Kalsi, P.; Pletzer, D.; Hancock, R.E.W. Murine Model of sinusitis infection for screening antimicrobial and immunomodulatory therapies. *Front. Cell Infect. Microbiol.* **2021**, *11*, 621081. [CrossRef]
109. Taghian, E.; Abtahi, S.H.; Mohammadi, A.; Hashemi, S.M.; Ahmadikia, K.; Dolatabadi, S.; Mohammadi, R. A study on the fungal rhinosinusitis: Causative agents, symptoms, and predisposing factors. *J. Res. Med. Sci.* **2023**, *28*, 12.
110. Montone, K.T. Pathology of fungal rhinosinusitis: A review. *Head Neck Pathol.* **2016**, *10*, 40–46. [CrossRef]
111. Chakrabarti, A.; Denning, D.W.; Ferguson, B.J.; Ponikau, J.; Buzina, W.; Kita, H.; Marple, B.; Panda, N.; Vlaminck, S.; Kauffmann-Lacroix, C.; et al. Fungal rhinosinusitis: A categorization and definitional schema addressing current controversies. *Laryngoscope* **2009**, *119*, 1809–1818. [CrossRef] [PubMed]
112. Deshazo, R.D. Syndromes of invasive fungal sinusitis. *Med. Mycol.* **2009**, *47* (Suppl. S1), S309–S314. [CrossRef]

113. deShazo, R.D.; O'Brien, M.; Chapin, K.; Soto-Aguilar, M.; Gardner, L.; Swain, R. A new classification and diagnostic criteria for invasive fungal sinusitis. *Arch. Otolaryngol. Head Neck Surg.* **1997**, *123*, 1181–1188. [CrossRef]
114. Raz, E.; Win, W.; Hagiwara, M.; Lui, Y.W.; Cohen, B.; Fatterpekar, G.M. Fungal Sinusitis. *Neuroimaging Clin. N. Am.* **2015**, *25*, 569–576. [CrossRef] [PubMed]
115. Deutsch, P.G.; Whittaker, J.; Prasad, S. Invasive and non-invasive fungal rhinosinusitis-a review and update of the evidence. *Medicina* **2019**, *55*, 319. [CrossRef]
116. Turner, J.H.; Soudry, E.; Nayak, J.V.; Hwang, P.H. Survival outcomes in acute invasive fungal sinusitis: A systematic review and quantitative synthesis of published evidence. *Laryngoscope* **2013**, *123*, 1112–1118. [CrossRef]
117. Montone, K.T.; Livolsi, V.A.; Feldman, M.D.; Palmer, J.; Chiu, A.G.; Lanza, D.C.; Kennedy, D.W.; Loevner, L.A.; Nachamkin, I. Fungal rhinosinusitis: A retrospective microbiologic and pathologic review of 400 patients at a single university medical center. *Int. J. Otolaryngol.* **2012**, *2012*, 684835. [CrossRef] [PubMed]
118. Zeng, M.; Zhou, X.; Yang, C.; Liu, Y.; Zhang, J.; Xin, C.; Qin, G.; Liu, F.; Song, Z. Comparative analysis of the biological characteristics and mechanisms of azole resistance of clinical *Aspergillus fumigatus* strains. *Front. Microbiol.* **2023**, *14*, 1253197. [CrossRef]
119. Shintani-Smith, S.; Luong, A.U.; Ramakrishnan, V.R.; Tan, B.K.; French, D.D.; Kern, R.C. Acute invasive fungal sinusitis: Epidemiology and outcomes in the United States. *Int. Forum Allergy Rhinol.* **2022**, *12*, 233–236. [CrossRef]
120. Chen, C.Y.; Sheng, W.H.; Cheng, A.; Chen, Y.C.; Tsay, W.; Tang, J.L.; Huang, S.Y.; Chang, S.C.; Tien, H.F. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. *BMC Infect. Dis.* **2011**, *11*, 250. [CrossRef]
121. Parikh, S.L.; Venkatraman, G.; DelGaudio, J.M. Invasive fungal sinusitis: A 15-year review from a single institution. *Am. J. Rhinol.* **2004**, *18*, 75–81. [CrossRef] [PubMed]
122. Craig, J.R. Updates in management of acute invasive fungal rhinosinusitis. *Curr. Opin. Otolaryngol. Head Neck Surg.* **2019**, *27*, 29–36. [CrossRef] [PubMed]
123. Erami, M.; Aboutalebian, S.; Hezaveh, S.J.H.; Ghazvini, R.D.; Momen-Heravi, M.; Jafari, Y.; Ahsaniarani, A.H.; Basirpour, B.; Matini, A.H.; Mirhendi, H. Microbial and clinical epidemiology of invasive fungal rhinosinusitis in hospitalized COVID-19 patients, the divergent causative agents. *Med. Mycol.* **2023**, *61*, myad020. [CrossRef] [PubMed]
124. Wandell, G.M.; Miller, C.; Rathor, A.; Wai, T.H.; Guyer, R.A.; Schmidt, R.A.; Turner, J.H.; Hwang, P.H.; Davis, G.E.; Humphreys, I.M. A multi-institutional review of outcomes in biopsy-proven acute invasive fungal sinusitis. *Int. Forum Allergy Rhinol.* **2018**, *8*, 1459–1468. [CrossRef] [PubMed]
125. Yin, L.X.; Spillinger, A.; Lees, K.A.; Bailey, K.R.; Choby, G.; O'Brien, E.K.; Stokken, J.K. An internally validated diagnostic tool for acute invasive fungal sinusitis. *Int. Forum Allergy Rhinol.* **2021**, *11*, 65–74. [CrossRef] [PubMed]
126. Drakos, P.E.; Nagler, A.; Or, R.; Naparstek, E.; Kapelushnik, J.; Engelhard, D.; Rahav, G.; Ne'eman, D.; Slavin, S. Invasive fungal sinusitis in patients undergoing bone marrow transplantation. *Bone Marrow Transplant.* **1993**, *12*, 203–208. [PubMed]
127. Zhang, Q.; Liu, F.; Zeng, M.; Zhang, J.; Liu, Y.; Xin, C.; Mao, Y.; Song, Z. Antifungal activity of sodium new houttuyfonate against *Aspergillus fumigatus* in vitro and in vivo. *Front. Microbiol.* **2022**, *13*, 856272. [CrossRef] [PubMed]
128. Payne, S.J.; Mitzner, R.; Kunchala, S.; Roland, L.; McGinn, J.D. Acute invasive fungal rhinosinusitis: A 15-year experience with 41 patients. *Otolaryngol. Head Neck Surg.* **2016**, *154*, 759–764. [CrossRef]
129. Gode, S.; Turhal, G.; Ozturk, K.; Aysel, A.; Midilli, R.; Karci, B. Acute invasive fungal rhinosinusitis: Survival analysis and the prognostic indicators. *Am. J. Rhinol. Allergy* **2015**, *29*, e164–e169. [CrossRef]
130. Fung, M.; Babik, J.; Humphreys, I.M.; Davis, G.E. Diagnosis and treatment of acute invasive fungal sinusitis in cancer and transplant patients. *Curr. Infect. Dis. Rep.* **2019**, *21*, 53. [CrossRef]
131. Davoudi, S.; Kumar, V.A.; Jiang, Y.; Kupferman, M.; Kontoyiannis, D.P. Invasive mould sinusitis in patients with haematological malignancies: A 10 year single-centre study. *J. Antimicrob. Chemother.* **2015**, *70*, 2899–2905. [CrossRef] [PubMed]
132. Silveira, M.L.C.; Anselmo-Lima, W.T.; Faria, F.M.; Queiroz, D.L.C.; Nogueira, R.L.; Leite, M.G.J.; Lessa, R.M.; Simões, B.P.; Tamashiro, E.; Valera, F.C.P. Impact of early detection of acute invasive fungal rhinosinusitis in immunocompromised patients. *BMC Infect. Dis.* **2019**, *19*, 310. [CrossRef] [PubMed]
133. Badiee, P.; Moghadami, M.; Rozbehani, H. Comparing immunological and molecular tests with conventional methods in diagnosis of acute invasive fungal rhinosinusitis. *J. Infect. Dev. Ctries.* **2016**, *10*, 90–95. [CrossRef] [PubMed]
134. Willinger, B.; Obradovic, A.; Selitsch, B.; Beck-Mannagetta, J.; Buzina, W.; Braun, H.; Apfalter, P.; Hirschl, A.M.; Makristathis, A.; Rotter, M. Detection and identification of fungi from fungus balls of the maxillary sinus by molecular techniques. *J. Clin. Microbiol.* **2003**, *41*, 581–585. [CrossRef] [PubMed]
135. Pham, A.S.; Tarrand, J.J.; May, G.S.; Lee, M.S.; Kontoyiannis, D.P.; Han, X.Y. Diagnosis of invasive mold infection by real-time quantitative PCR. *Am. J. Clin. Pathol.* **2003**, *119*, 38–44. [CrossRef] [PubMed]
136. Melancon, C.C.; Lindsey, J.; Russell, G.B.; Clinger, J.D. The role of galactomannan Aspergillus antigen in diagnosing acute invasive fungal sinusitis. *Int. Forum Allergy Rhinol.* **2019**, *9*, 60–66. [CrossRef] [PubMed]
137. Navuluri, S.; Gardner, J.R.; Vickers, D.; Mohler, S.; King, D.; Kanaan, A. Risk Stratification of acute invasive fungal rhinosinusitis in patients with hematologic pathology. *Laryngoscope* **2023**, *133*, 1059–1064. [CrossRef] [PubMed]
138. Cho, H.J.; Jang, M.S.; Hong, S.D.; Chung, S.K.; Kim, H.Y.; Dhong, H.J. Prognostic factors for survival in patients with acute invasive fungal rhinosinusitis. *Am. J. Rhinol. Allergy* **2015**, *29*, 48–53. [CrossRef] [PubMed]

139. DelGaudio, J.M.; Swain, R.E., Jr.; Kingdom, T.T.; Muller, S.; Hudgins, P.A. Computed tomographic findings in patients with invasive fungal sinusitis. *Arch. Otolaryngol. Head Neck Surg.* **2003**, *129*, 236–240. [CrossRef] [PubMed]
140. Groppo, E.R.; El-Sayed, I.H.; Aiken, A.H.; Glastonbury, C.M. Computed tomography and magnetic resonance imaging characteristics of acute invasive fungal sinusitis. *Arch. Otolaryngol. Head Neck Surg.* **2011**, *137*, 1005–1010. [CrossRef]
141. Valera, F.C.; do Lago, T.; Tamashiro, E.; Yassuda, C.C.; Silveira, F.; Anselmo-Lima, W.T. Prognosis of acute invasive fungal rhinosinusitis related to underlying disease. *Int. J. Infect. Dis.* **2011**, *15*, e841–e844. [CrossRef] [PubMed]
142. Crist, H.; Hennessy, M.; Hodos, J.; McGinn, J.; White, B.; Payne, S.; Warrick, J.I. Acute invasive fungal rhinosinusitis: Frozen section histomorphology and diagnosis with PAS stain. *Head Neck Pathol.* **2019**, *13*, 318–326. [CrossRef] [PubMed]
143. Kim, D.H.; Kim, S.W.; Hwang, S.H. Usefulness of intraoperative frozen section for diagnosing acute invasive fungal rhinosinusitis: A systematic review and meta-analysis. *Int. Forum Allergy Rhinol.* **2021**, *11*, 1347–1354. [CrossRef] [PubMed]
144. Hennessy, M.; McGinn, J.; White, B.; Payne, S.; Warrick, J.I.; Crist, H. Frozen section as a rapid and accurate method for diagnosing acute invasive fungal rhinosinusitis. *Otolaryngol. Head Neck Surg.* **2018**, *159*, 576–580. [CrossRef] [PubMed]
145. Shamsaei, S.; Falahati, M.; Farahyar, S.; Raiesi, O.; Haghighi, L.; Eraghiye Farahani, H.; Akhavan, A.; Shamsaie, A.; Yarahmadi, M.; Keymaram, M. Acute invasive fungal rhinosinusitis: Molecular identification and update in management of frozen section biopsy. *Microb. Pathog.* **2021**, *159*, 105125. [CrossRef] [PubMed]
146. Malleshappa, V.; Rupa, V.; Varghese, L.; Kurien, R. Avoiding repeated surgery in patients with acute invasive fungal sinusitis. *Eur. Arch. Otorhinolaryngol.* **2020**, *277*, 1667–1674. [CrossRef] [PubMed]
147. Kasapoglu, F.; Coskun, H.; Ozmen, O.A.; Akalin, H.; Ener, B. Acute invasive fungal rhinosinusitis: Evaluation of 26 patients treated with endonasal or open surgical procedures. *Otolaryngol. Head Neck Surg.* **2010**, *143*, 614–620. [CrossRef] [PubMed]
148. Monroe, M.M.; McLean, M.; Sautter, N.; Wax, M.K.; Andersen, P.E.; Smith, T.L.; Gross, N.D. Invasive fungal rhinosinusitis: A 15-year experience with 29 patients. *Laryngoscope* **2013**, *123*, 1583–1587. [CrossRef] [PubMed]
149. DelGaudio, J.M.; Clemson, L.A. An early detection protocol for invasive fungal sinusitis in neutropenic patients successfully reduces extent of disease at presentation and long term morbidity. *Laryngoscope* **2009**, *119*, 180–183. [CrossRef] [PubMed]
150. Bala, K.; Chander, J.; Handa, U.; Punia, R.S.; Attri, A.K. A prospective study of mucormycosis in north India: Experience from a tertiary care hospital. *Med. Mycol.* **2015**, *53*, 248–257. [CrossRef]
151. Roden, M.M.; Zaoutis, T.E.; Buchanan, W.L.; Knudsen, T.A.; Sarkisova, T.A.; Schaufele, R.L.; Sein, M.; Sein, T.; Chiou, C.C.; Chu, J.H.; et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. *Clin. Infect. Dis.* **2005**, *41*, 634–653. [CrossRef]
152. Ahmed, Y.; Delaney, S.; Markarian, A. Successful Isavuconazole therapy in a patient with acute invasive fungal rhinosinusitis and acquired immune deficiency syndrome. *Am. J. Otolaryngol.* **2016**, *37*, 152–155. [CrossRef]
153. Kennedy, C.A.; Adams, G.L.; Neglia, J.P.; Giebink, G.S. Impact of surgical treatment on paranasal fungal infections in bone marrow transplant patients. *Otolaryngol. Head Neck Surg.* **1997**, *116*, 610–616. [CrossRef]
154. Stringer, S.P.; Ryan, M.W. Chronic invasive fungal rhinosinusitis. *Otolaryngol. Clin. N. Am.* **2000**, *33*, 375–387. [CrossRef]
155. D'Anza, B.; Stokken, J.; Greene, J.S.; Kennedy, T.; Woodard, T.D.; Sindwani, R. Chronic invasive fungal sinusitis: Characterization and shift in management of a rare disease. *Int. Forum Allergy Rhinol.* **2016**, *6*, 1294–1300. [CrossRef]
156. Zhou, L.H.; Wang, X.; Wang, R.Y.; Zhao, H.Z.; Jiang, Y.K.; Cheng, J.H.; Huang, L.P.; Chen, Z.Q.; Wang, D.H.; Zhu, L.P. Entities of chronic and granulomatous invasive fungal rhinosinusitis: Separate or not? *Open Forum Infect. Dis.* **2018**, *5*, ofy228. [CrossRef]
157. Vakharia, K.T.; Durand, M.L.; Hamilos, D.L.; Geyer, J.T.; Holbrook, E.H. An atypical case of chronic invasive fungal sinusitis and its management. *Otolaryngol. Head Neck Surg.* **2010**, *142*, 150–151. [CrossRef]
158. Alotaibi, N.H.; Omar, O.A.; Altahan, M.; Alsheikh, H.; Al Mana, F.; Mahasin, Z.; Othman, E. Chronic invasive fungal rhinosinusitis in immunocompetent patients: A retrospective chart review. *Front. Surg.* **2020**, *7*, 608342. [CrossRef]
159. Swami, T.; Pannu, S.; Kumar, M.; Gupta, G. Chronic invasive fungal rhinosinusitis by *Paecilomyces variotii*: A rare case report. *Indian. J. Med. Microbiol.* **2016**, *34*, 103–106. [CrossRef]
160. Aribandi, M.; McCoy, V.A.; Bazan, C., III. Imaging features of invasive and noninvasive fungal sinusitis: A review. *Radiographics* **2007**, *27*, 1283–1296. [CrossRef]
161. Challa, S.; Uppin, S.G.; Hanumanthu, S.; Panigrahi, M.K.; Purohit, A.K.; Sattaluri, S.; Borgohain, R.; Chava, A.; Vemu, L.; Jagarlapudi, M.M. Fungal rhinosinusitis: A clinicopathological study from South India. *Eur. Arch. Otorhinolaryngol.* **2010**, *267*, 1239–1245. [CrossRef]
162. Dykewicz, M.S.; Rodrigues, J.M.; Slavin, R.G. Allergic fungal rhinosinusitis. *J. Allergy Clin. Immunol.* **2018**, *142*, 341–351. [CrossRef]
163. Tyler, M.A.; Luong, A.U. Current understanding of allergic fungal rhinosinusitis. *World J. Otorhinolaryngol. Head Neck Surg.* **2018**, *4*, 179–185. [CrossRef]
164. Kupferberg, S.B.; Bent, J.P., III; Kuhn, F.A. Prognosis for allergic fungal sinusitis. *Otolaryngol. Head Neck Surg.* **1997**, *117*, 35–41. [CrossRef]
165. Callejas, C.A.; Douglas, R.G. Fungal rhinosinusitis: What every allergist should know. *Clin. Exp. Allergy* **2013**, *43*, 835–849. [CrossRef]
166. Luong, A.U.; Chua, A.; Alim, B.M.; Olsson, P.; Javer, A. Allergic fungal rhinosinusitis: The role and expectations of biologics. *J. Allergy Clin. Immunol. Pract.* **2022**, *10*, 3156–3162. [CrossRef]

167. Tyler, M.A.; Russell, C.B.; Smith, D.E.; Rottman, J.B.; Padro Dietz, C.J.; Hu, X.; Citardi, M.J.; Fakhri, S.; Assassi, S.; Luong, A. Large-scale gene expression profiling reveals distinct type 2 inflammatory patterns in chronic rhinosinusitis subtypes. *J. Allergy Clin. Immunol.* **2017**, *139*, 1061–1064.e1064. [CrossRef]
168. Mabry, R.L.; Manning, S. Radioallergosorbent microscreen and total immunoglobulin E in allergic fungal sinusitis. *Otolaryngol. Head Neck Surg.* **1995**, *113*, 721–723. [CrossRef]
169. Manning, S.C.; Holman, M. Further evidence for allergic pathophysiology in allergic fungal sinusitis. *Laryngoscope* **1998**, *108*, 1485–1496. [CrossRef]
170. Mabry, R.L.; Marple, B.F.; Folker, R.J.; Mabry, C.S. Immunotherapy for allergic fungal sinusitis: Three years' experience. *Otolaryngol. Head Neck Surg.* **1998**, *119*, 648–651. [CrossRef]
171. Collins, M.; Nair, S.; Smith, W.; Kette, F.; Gillis, D.; Wormald, P.J. Role of local immunoglobulin E production in the pathophysiology of noninvasive fungal sinusitis. *Laryngoscope* **2004**, *114*, 1242–1246. [CrossRef]
172. Porter, P.C.; Lim, D.J.; Maskatia, Z.K.; Mak, G.; Tsai, C.L.; Citardi, M.J.; Fakhri, S.; Shaw, J.L.; Fothergil, A.; Kheradmand, F.; et al. Airway surface mycosis in chronic TH2-associated airway disease. *J. Allergy Clin. Immunol.* **2014**, *134*, 325–331. [CrossRef]
173. Pant, H.; Beroukas, D.; Kette, F.E.; Smith, W.B.; Wormald, P.J.; Macardle, P.J. Nasal polyp cell populations and fungal-specific peripheral blood lymphocyte proliferation in allergic fungal sinusitis. *Am. J. Rhinol. Allergy* **2009**, *23*, 453–460. [CrossRef]
174. Pant, H.; Kette, F.E.; Smith, W.B.; Macardle, P.J.; Wormald, P.J. Eosinophilic mucus chronic rhinosinusitis: Clinical subgroups or a homogeneous pathogenic entity? *Laryngoscope* **2006**, *116*, 1241–1247. [CrossRef]
175. Pant, H.; Kette, F.E.; Smith, W.B.; Wormald, P.J.; Macardle, P.J. Fungal-specific humoral response in eosinophilic mucus chronic rhinosinusitis. *Laryngoscope* **2005**, *115*, 601–606. [CrossRef]
176. Carney, A.S.; Tan, L.W.; Adams, D.; Varelias, A.; Ooi, E.H.; Wormald, P.J. Th2 immunological inflammation in allergic fungal sinusitis, nonallergic eosinophilic fungal sinusitis, and chronic rhinosinusitis. *Am. J. Rhinol.* **2006**, *20*, 145–149. [CrossRef]
177. Den Beste, K.A.; Hoddeson, E.K.; Parkos, C.A.; Nusrat, A.; Wise, S.K. Epithelial permeability alterations in an in vitro air-liquid interface model of allergic fungal rhinosinusitis. *Int. Forum Allergy Rhinol.* **2013**, *3*, 19–25. [CrossRef]
178. Celebi Sözener, Z.; Cevhertas, L.; Nadeau, K.; Akdis, M.; Akdis, C.A. Environmental factors in epithelial barrier dysfunction. *J. Allergy Clin. Immunol.* **2020**, *145*, 1517–1528. [CrossRef]
179. Chen, J.C.; Chuang, J.G.; Su, Y.Y.; Chiang, B.L.; Lin, Y.S.; Chow, L.P. The protease allergen Pen c 13 induces allergic airway inflammation and changes in epithelial barrier integrity and function in a murine model. *J. Biol. Chem.* **2011**, *286*, 26667–26679. [CrossRef]
180. Tieu, D.D.; Kern, R.C.; Schleimer, R.P. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. *J. Allergy Clin. Immunol.* **2009**, *124*, 37–42. [CrossRef]
181. Lane, A.P. The role of innate immunity in the pathogenesis of chronic rhinosinusitis. *Curr. Allergy Asthma Rep.* **2009**, *9*, 205–212. [CrossRef]
182. Psaltis, A.J.; Bruhn, M.A.; Ooi, E.H.; Tan, L.W.; Wormald, P.J. Nasal mucosa expression of lactoferrin in patients with chronic rhinosinusitis. *Laryngoscope* **2007**, *117*, 2030–2035. [CrossRef]
183. Wright, J.R. Host defense functions of pulmonary surfactant. *Biol. Neonate* **2004**, *85*, 326–332. [CrossRef] [PubMed]
184. Ooi, E.H.; Wormald, P.J.; Carney, A.S.; James, C.L.; Tan, L.W. Surfactant protein d expression in chronic rhinosinusitis patients and immune responses in vitro to Aspergillus and alternaria in a nasal explant model. *Laryngoscope* **2007**, *117*, 51–57. [CrossRef]
185. Tyler, M.A.; Padro Dietz, C.J.; Russell, C.B.; Citardi, M.J.; Assassi, S.; Ying, J.; Luong, A.U. Distinguishing molecular features of allergic fungal rhinosinusitis. *Otolaryngol. Head Neck Surg.* **2018**, *159*, 185–193. [CrossRef] [PubMed]
186. Nagarkar, D.R.; Poposki, J.A.; Tan, B.K.; Comeau, M.R.; Peters, A.T.; Hulse, K.E.; Suh, L.A.; Norton, J.; Harris, K.E.; Grammer, L.C.; et al. Thymic stromal lymphopoietin activity is increased in nasal polyps of patients with chronic rhinosinusitis. *J. Allergy Clin. Immunol.* **2013**, *132*, 593–600.e512. [CrossRef]
187. Borowczyk, J.; Shutova, M.; Brembilla, N.C.; Boehncke, W.H. IL-25 (IL-17E) in epithelial immunology and pathophysiology. *J. Allergy Clin. Immunol.* **2021**, *148*, 40–52. [CrossRef]
188. Kohanski, M.A.; Workman, A.D.; Patel, N.N.; Hung, L.Y.; Shtraks, J.P.; Chen, B.; Blasetti, M.; Doghramji, L.; Kennedy, D.W.; Adappa, N.D.; et al. Solitary chemosensory cells are a primary epithelial source of IL-25 in patients with chronic rhinosinusitis with nasal polyps. *J. Allergy Clin. Immunol.* **2018**, *142*, 460–469.e467. [CrossRef] [PubMed]
189. Patel, N.N.; Kohanski, M.A.; Maina, I.W.; Triantafillou, V.; Workman, A.D.; Tong, C.C.L.; Kuan, E.C.; Bosso, J.V.; Adappa, N.D.; Palmer, J.N.; et al. Solitary chemosensory cells producing interleukin-25 and group-2 innate lymphoid cells are enriched in chronic rhinosinusitis with nasal polyps. *Int. Forum Allergy Rhinol.* **2018**, *8*, 900–906. [CrossRef]
190. Toki, S.; Goleniewska, K.; Zhang, J.; Zhou, W.; Newcomb, D.C.; Zhou, B.; Kita, H.; Boyd, K.L.; Peebles, R.S., Jr. TSLP and IL-33 reciprocally promote each other's lung protein expression and ILC2 receptor expression to enhance innate type-2 airway inflammation. *Allergy* **2020**, *75*, 1606–1617. [CrossRef]
191. Iijima, K.; Kobayashi, T.; Hara, K.; Kephart, G.M.; Ziegler, S.F.; McKenzie, A.N.; Kita, H. IL-33 and thymic stromal lymphopoietin mediate immune pathology in response to chronic airborne allergen exposure. *J. Immunol.* **2014**, *193*, 1549–1559. [CrossRef] [PubMed]
192. Sugita, K.; Steer, C.A.; Martinez-Gonzalez, I.; Altunbulakli, C.; Morita, H.; Castro-Giner, F.; Kubo, T.; Wawrzyniak, P.; Rückert, B.; Sudo, K.; et al. Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients. *J. Allergy Clin. Immunol.* **2018**, *141*, 300–310.e311. [CrossRef]

193. Wawrzyniak, P.; Wawrzyniak, M.; Wanke, K.; Sokolowska, M.; Bendelja, K.; Rückert, B.; Globinska, A.; Jakiela, B.; Kast, J.I.; Idzko, M.; et al. Regulation of bronchial epithelial barrier integrity by type 2 cytokines and histone deacetylases in asthmatic patients. *J. Allergy Clin. Immunol.* **2017**, *139*, 93–103. [CrossRef]
194. Maeda, K.; Caldez, M.J.; Akira, S. Innate immunity in allergy. *Allergy* **2019**, *74*, 1660–1674. [CrossRef] [PubMed]
195. Watts, A.M.; Cripps, A.W.; West, N.P.; Cox, A.J. Modulation of allergic inflammation in the nasal mucosa of allergic rhinitis sufferers with topical pharmaceutical agents. *Front. Pharmacol.* **2019**, *10*, 294. [CrossRef] [PubMed]
196. Kirsche, H.; Niederführ, A.; Deutschle, T.; Fuchs, C.; Riechelmann, H. Ratio of myeloid and plasmacytoid dendritic cells and TH2 skew in CRS with nasal polyps. *Allergy* **2010**, *65*, 24–31. [CrossRef]
197. Tai, J.; Kwak, J.; Han, M.; Kim, T.H. Different roles of dendritic cells for chronic rhinosinusitis treatment according to phenotype. *Int. J. Mol. Sci.* **2022**, *23*, 8032. [CrossRef]
198. Katsoulis-Dimitriou, K.; Kotrba, J.; Voss, M.; Dudeck, J.; Dudeck, A. Mast cell functions linking innate sensing to adaptive immunity. *Cells* **2020**, *9*, 2538. [CrossRef] [PubMed]
199. Xie, Y.; Zhou, X.; Zhang, J.; Yu, H.; Song, Z. Immunomodulatory responses of differentially polarized macrophages to fungal infections. *Int. Immunopharmacol.* **2022**, *111*, 109089. [CrossRef]
200. Chua, A.J.; Jafar, A.; Luong, A.U. Update on allergic fungal rhinosinusitis. *Ann. Allergy Asthma Immunol.* **2023**, *131*, 300–306. [CrossRef]
201. Dietz, C.J.; Sun, H.; Yao, W.C.; Citardi, M.J.; Corry, D.B.; Luong, A.U. *Aspergillus fumigatus* induction of IL-33 expression in chronic rhinosinusitis is PAR2-dependent. *Laryngoscope* **2019**, *129*, 2230–2235. [CrossRef]
202. Patel, N.N.; Triantafillou, V.; Maina, I.W.; Workman, A.D.; Tong, C.C.L.; Kuan, E.C.; Papagiannopoulos, P.; Bosso, J.V.; Adappa, N.D.; Palmer, J.N.; et al. Fungal extracts stimulate solitary chemosensory cell expansion in noninvasive fungal rhinosinusitis. *Int. Forum Allergy Rhinol.* **2019**, *9*, 730–737. [CrossRef]
203. Hutcheson, P.S.; Schubert, M.S.; Slavin, R.G. Distinctions between allergic fungal rhinosinusitis and chronic rhinosinusitis. *Am. J. Rhinol. Allergy* **2010**, *24*, 405–408. [CrossRef] [PubMed]
204. Salamah, M.A.; Alsarraj, M.; Alsolami, N.; Hanbazazah, K.; Alharbi, A.M.; Khalifah, W., Sr. Clinical, radiological, and histopathological patterns of allergic fungal sinusitis: A single-center retrospective study. *Cureus* **2020**, *12*, e9233. [CrossRef]
205. Zinreich, S.J.; Kennedy, D.W.; Malat, J.; Curtin, H.D.; Epstein, J.I.; Huff, L.C.; Kumar, A.J.; Johns, M.E.; Rosenbaum, A.E. Fungal sinusitis: Diagnosis with CT and MR imaging. *Radiology* **1988**, *169*, 439–444. [CrossRef]
206. Rodrigues, J.; Caruthers, C.; Azmeh, R.; Dykewicz, M.S.; Slavin, R.G.; Knutsen, A.P. The spectrum of allergic fungal diseases of the upper and lower airways. *Expert. Rev. Clin. Immunol.* **2016**, *12*, 531–550. [CrossRef]
207. El-Morsy, S.M.; Khafagy, Y.W.; El-Naggar, M.M.; Beih, A.A. Allergic fungal rhinosinusitis: Detection of fungal DNA in sinus aspirate using polymerase chain reaction. *J. Laryngol. Otol.* **2010**, *124*, 152–160. [CrossRef]
208. Schubert, M.S.; Hutcheson, P.S.; Graff, R.J.; Santiago, L.; Slavin, R.G. HLA-DQB1 *03 in allergic fungal sinusitis and other chronic hypertrophic rhinosinusitis disorders. *J. Allergy Clin. Immunol.* **2004**, *114*, 1376–1383. [CrossRef] [PubMed]
209. White, L.C.; Jang, D.W.; Yelvertan, J.C.; Kountakis, S.E. Bony erosion patterns in patients with allergic fungal sinusitis. *Am. J. Rhinol. Allergy* **2015**, *29*, 243–245. [CrossRef]
210. Bent, J.P., III; Kuhn, F.A. Diagnosis of allergic fungal sinusitis. *Otolaryngol. Head Neck Surg.* **1994**, *111*, 580–588. [CrossRef] [PubMed]
211. Kuhn, F.A.; Javer, A.R. Allergic fungal rhinosinusitis: Perioperative management, prevention of recurrence, and role of steroids and antifungal agents. *Otolaryngol. Clin. N. Am.* **2000**, *33*, 419–433. [CrossRef] [PubMed]
212. Han, J.K.; Kern, R.C. Topical therapies for management of chronic rhinosinusitis: Steroid implants. *Int. Forum Allergy Rhinol.* **2019**, *9*, S22–S26. [CrossRef] [PubMed]
213. Hoffman, V.; Mortimer, K.M.; Mulder, K.; Topuria, I.; Gliklich, R.; Kallman, J.E. Real-world evidence analysis of the impact of steroid-eluting implants on healthcare resource use among chronic rhinosinusitis patients undergoing sinus surgery. *Curr. Med. Res. Opin.* **2022**, *38*, 375–381. [CrossRef]
214. Rudmik, L.; Hoy, M.; Schlosser, R.J.; Harvey, R.J.; Welch, K.C.; Lund, V.; Smith, T.L. Topical therapies in the management of chronic rhinosinusitis: An evidence-based review with recommendations. *Int. Forum Allergy Rhinol.* **2013**, *3*, 281–298. [CrossRef]
215. Rojita, M.; Samal, S.; Pradhan, P.; Venkatachalam, V.P. Comparison of Steroid and Itraconazole for Prevention of Recurrence in Allergic Fungal Rhinosinusitis: A Randomized Controlled Trial. *J. Clin. Diagn. Res.* **2017**, *11*, mc01–mc03. [CrossRef]
216. Salil, A.; Joy, N.; Faizal, B. A prospective study comparing itraconazole alone versus systemic steroids alone as adjuncts to topical steroids in the post-operative management of allergic fungal rhinosinusitis. *Clin. Otolaryngol.* **2023**, *48*, 356–362. [CrossRef] [PubMed]
217. Verma, R.K.; Patro, S.K.; Francis, A.A.; Panda, N.K.; Chakrabarti, A.; Singh, P. Role of preoperative versus postoperative itraconazole in allergic fungal rhinosinusitis. *Med. Mycol.* **2017**, *55*, 614–623. [CrossRef]
218. Khalil, Y.; Tharwat, A.; Abdou, A.G.; Essa, E.; Elsawy, A.H.; Elnakib, O.; Elnaidany, N.F. The role of antifungal therapy in the prevention of recurrent allergic fungal rhinosinusitis after functional endoscopic sinus surgery: A randomized, controlled study. *Ear Nose Throat J.* **2011**, *90*, E1–E7. [CrossRef]
219. Head, K.; Sharp, S.; Chong, L.Y.; Hopkins, C.; Philpott, C. Topical and systemic antifungal therapy for chronic rhinosinusitis. *Cochrane Database Syst. Rev.* **2018**, *9*, Cd012453. [CrossRef]

220. Mabry, R.L.; Manning, S.C.; Mabry, C.S. Immunotherapy in the treatment of allergic fungal sinusitis. *Otolaryngol. Head Neck Surg.* **1997**, *116*, 31–35. [PubMed]
221. Mabry, R.L.; Mabry, C.S. Immunotherapy for allergic fungal sinusitis: The second year. *Otolaryngol. Head Neck Surg.* **1997**, *117*, 367–371. [CrossRef]
222. Mabry, R.L.; Marple, B.F.; Mabry, C.S. Outcomes after discontinuing immunotherapy for allergic fungal sinusitis. *Otolaryngol. Head Neck Surg.* **2000**, *122*, 104–106. [CrossRef]
223. Folker, R.J.; Marple, B.F.; Mabry, R.L.; Mabry, C.S. Treatment of allergic fungal sinusitis: A comparison trial of postoperative immunotherapy with specific fungal antigens. *Laryngoscope* **1998**, *108*, 1623–1627. [CrossRef] [PubMed]
224. Greenhaw, B.; deShazo, R.D.; Arnold, J.; Wright, L. Fungal immunotherapy in patients with allergic fungal sinusitis. *Ann. Allergy Asthma Immunol.* **2011**, *107*, 432–436. [CrossRef] [PubMed]
225. Hall, A.G.; deShazo, R.D. Immunotherapy for allergic fungal sinusitis. *Curr. Opin. Allergy Clin. Immunol.* **2012**, *12*, 629–634. [CrossRef]
226. Gan, E.C.; Thamboo, A.; Rudmik, L.; Hwang, P.H.; Ferguson, B.J.; Javer, A.R. Medical management of allergic fungal rhinosinusitis following endoscopic sinus surgery: An evidence-based review and recommendations. *Int. Forum Allergy Rhinol.* **2014**, *4*, 702–715. [CrossRef] [PubMed]
227. Grosjean, P.; Weber, R. Fungus balls of the paranasal sinuses: A review. *Eur. Arch. Otorhinolaryngol.* **2007**, *264*, 461–470. [CrossRef] [PubMed]
228. Ferguson, B.J. Definitions of fungal rhinosinusitis. *Otolaryngol. Clin. N. Am.* **2000**, *33*, 227–235. [CrossRef] [PubMed]
229. Pagella, F.; Matti, E.; De Bernardi, F.; Semino, L.; Cavanna, C.; Marone, P.; Farina, C.; Castelnuovo, P. Paranasal sinus fungus ball: Diagnosis and management. *Mycoses* **2007**, *50*, 451–456. [CrossRef]
230. Klossek, J.M.; Serrano, E.; Péloquin, L.; Percodani, J.; Fontanel, J.P.; Pessey, J.J. Functional endoscopic sinus surgery and 109 mycetomas of paranasal sinuses. *Laryngoscope* **1997**, *107*, 112–117. [CrossRef]
231. Dufour, X.; Kauffmann-Lacroix, C.; Ferrie, J.C.; Goujon, J.M.; Rodier, M.H.; Karkas, A.; Klossek, J.M. Paranasal sinus fungus ball and surgery: A review of 175 cases. *Rhinology* **2005**, *43*, 34–39.
232. Assiri, A.M.; Ryu, S.; Kim, J.H. Concurrent diagnosis of sinus fungus ball and invasive fungal sinusitis: A retrospective case series. *Mycoses* **2021**, *64*, 1117–1123. [CrossRef]
233. Shin, J.M.; Baek, B.J.; Byun, J.Y.; Jun, Y.J.; Lee, J.Y. Analysis of sinonasal anatomical variations associated with maxillary sinus fungal balls. *Auris Nasus Larynx* **2016**, *43*, 524–528. [CrossRef] [PubMed]
234. Basurrah, M.; Lee, I.H.; Kim, D.H.; Kim, S.W.; Kim, S.W. Anatomical variations associated with maxillary sinus fungal ball. *Ear Nose Throat J.* **2023**, *102*, 727–732. [CrossRef] [PubMed]
235. Mensi, M.; Piccioni, M.; Marsili, F.; Nicolai, P.; Sapelli, P.L.; Latronico, N. Risk of maxillary fungus ball in patients with endodontic treatment on maxillary teeth: A case-control study. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.* **2007**, *103*, 433–436. [CrossRef]
236. deShazo, R.D.; O'Brien, M.; Chapin, K.; Soto-Aguilar, M.; Swain, R.; Lyons, M.; Bryars, W.C., Jr.; Alsip, S. Criteria for the diagnosis of sinus mycetoma. *J. Allergy Clin. Immunol.* **1997**, *99*, 475–485. [CrossRef] [PubMed]
237. Cho, D.Y.; Hunter, R.C.; Ramakrishnan, V.R. The Microbiome and chronic rhinosinusitis. *Immunol. Allergy Clin. N. Am.* **2020**, *40*, 251–263. [CrossRef]
238. Lee, J.T.; Simpson, C.A.; Yang, H.H.; Suh, J.D.; Wang, M.B.; Lagishetty, V.; Liang, F.; Jacobs, J.P. Fungal and bacterial microbiome in sinus mucosa of patients with and without chronic rhinosinusitis. *Laryngoscope* **2024**, *134*, 1054–1062. [CrossRef]
239. Rawlings, B.A.; Higgins, T.S.; Han, J.K. Bacterial pathogens in the nasopharynx, nasal cavity, and osteomeatal complex during wellness and viral infection. *Am. J. Rhinol. Allergy* **2013**, *27*, 39–42. [CrossRef]
240. Jun, Y.J.; Shin, J.M.; Lee, J.Y.; Baek, B.J. Bony changes in a unilateral maxillary sinus fungal ball. *J. Craniofac Surg.* **2018**, *29*, e44–e47. [CrossRef]

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