The role of viruses in the inception of sinusitis

Hyeon Seung Lee¹, Sophia J Volpe¹, Eugene H Chang¹

¹ Department of Otolaryngology, University of Arizona, Tucson, Arizona, USA

Corresponding author: Eugene H Chang, University of Arizona College of Medicine – Tucson Department of Otolaryngology, 1501 N. Campbell Avenue, PO Box 245074, Tucson, AZ 85724

Tel: (520) 626-7859, Fax: (520) 626-6995, Email: echang@oto.arizona.edu

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Highlights

- The four commonly isolated viruses in patients with chronic rhinosinusitis are rhinovirus, parainfluenza virus, influenza virus, and respiratory syncytial virus.
- Viral infection in the upper airways was shown to degrade epithelial barrier function, and rhinovirus infection has been specifically shown to degrade tight junction and adherens junction components.
- Age is strongly associated with CRS risk. Viral infections linked with CRS are more prevalent in infants and children than adults.
Abstract (structured):

**Introduction.** Chronic rhinosinusitis (CRS) is a complex inflammatory disorder that affects between 2 and 16% of adults in the United States with estimated healthcare costs between 4 to 12 million USD. Viruses are a frequent cause of upper respiratory infections and a trigger for CRS exacerbations.

**What viruses are seen in CRS?** There are several cross-sectional studies that have identified types of viruses associated with CRS. Rhinovirus, parainfluenza virus, influenza virus, and respiratory syncytial virus were the main associated viruses found in nasal lavage samples of patients with CRS. Other viruses such as adenovirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have weak associations with CRS and were excluded from the review.

**Virus receptors and targets in the upper airway.** Rhinovirus and its subtypes utilize glycoproteins like intercellular adhesion molecule 1 (ICAM-1), low density lipoprotein receptor (LDLR) family members, and cadherin-related family member 3 (CDHR3) to invade host cells. Influenza and parainfluenza virus invade through the binding of hemagglutinin (HA) to sialic acid-containing molecules while respiratory syncytial virus has a RSV specific glycoprotein that binds to the cellular receptor human nucleolin (NCL).

**Immunologic responses to viruses.** Viral infection that causes CRS is frequently associated with type 1 and type 2 immune responses. Dysregulated immune response to viral infections can result in the activation of airway remodeling, epithelial-mesenchymal transitions, and epithelial barrier breakdown that are central to the pathogenesis of CRS.
**Risk factors for viral infections in CRS.** Dysfunctional epithelial barrier function and age are strong risk factors for CRS infections. Comorbid respiratory diseases like asthma or allergic rhinitis are highly associated with CRS risk and CRS exacerbations. **CRS related viruses in Children vs Adults.** Children are more likely to have upper respiratory tract infections than adults and viruses associated with CRS are more prevalent in infants and children. **Conclusion.** Studying and understanding the role of viruses in CRS is an important step in identifying disease pathogenesis and targeting these pathways early to slow disease progression.

**Abstract (unstructured):** Chronic rhinosinusitis (CRS) is a complex inflammatory disorder that affects between 2 to 16% of adults in the United States with estimated healthcare costs between 4 to 12 million USD. Viruses are a frequent etiologic factor for URIs, frequently identified in the sinuses of patients with CRS as well as a trigger for CRS exacerbations. Therefore, investigating the role of viruses provides an opportunity to identify their role in the pathogenesis of CRS. In this review, we identified the viruses frequently isolated in patients with CRS, as well as their associated immunologic responses and contributions to inflammation. Rhinovirus, parainfluenza, influenza, and respiratory syncytial virus as the viruses commonly found in patients with CRS. This information allows us to target pathways early in the pathogenesis of diseases, thereby playing a significant role in slowing the progression of this chronic disease. **Keywords.** Chronic rhinosinusitis, Rhinovirus, Parainfluenza virus, Influenza virus, Respiratory Syncytial virus
Introduction

Studies on the pathogenesis of chronic rhinosinusitis (CRS) are challenging, as they require longitudinal cohorts and analyses prior to the onset of disease. Although significant findings have been made in the pathophysiology of CRS, the majority of these studies have been retrospective or cross-sectional. However, many CRS patients subjectively recall that their symptoms began with an upper respiratory infection (URI) that progressively became more severe and chronic in nature. URIs are common viral infections affecting the nose, throat, and airways, and can last between 7 and 11 days. In some patients, a URI can progress into acute rhinosinusitis (ARS). ARS features an increase in severity of symptoms lasting greater than 10 days and is frequently associated with facial pain/tenderness, hyposmia/anosmia, nasal obstruction and mucopurulent drainage. In select cases, these symptoms persist for at least 12 consecutive weeks and meet the criteria of CRS (Table 1) [1]. CRS is a complex inflammatory disorder that affects between 2% and 16% of adults in the United States with estimated healthcare costs between $4 to $12 million USD [2][3]

Viruses are a frequent etiologic factor for URIs, frequently identified in the sinuses of patients with CRS, and a trigger for CRS exacerbations [4]. Therefore, investigating the role of viruses provides an opportunity to identify its role in the pathogenesis of CRS. In this review article, we will discuss the role of viruses and their associated immunologic responses and contributions to inflammation of CRS. This information may allow us to target pathways early in the pathogenesis of diseases, thereby playing a significant role in slowing the progression of this chronic disease.

What viruses are seen in CRS?
There are several cross-sectional studies that have identified the types of viruses associated with CRS. In a study done by Cho et al, researchers found that CRS patients had higher proportions of respiratory viruses in their nasal secretions than the control group of patients without CRS. Of the viruses identified, rhinovirus (RV) infection in lavage and mucosal samples was significantly associated with CRS patients compared to controls [4]. In the same study by Cho et al, parainfluenza, influenza and respiratory syncytial viruses (RSV) were all also found in the nasal lavage samples of patients with CRS. However, only rhinovirus and parainfluenza virus were detected at higher rates among CRS patients compared to the control group [4]. In another study by Ramadan et al., PCR confirmed that 20% of the CRS patients' samples were positive for RSV RNA, but none were positive for adenoviral DNA [5]. In a third study by Abshirini et al., RT-PCR results showed 28.94% of their sample size of patients with CRS had rhinovirus and 11.84% had RSV [6]. One of the most significant pathogens in terms of CRS is Human Rhinovirus (HRV). HRVs are frequently identified as viruses in the common cold as well as in CRS. There are three main subgroups of HRV which are referred to as HRV-A, HRV-B, and HRV-C [7]. However, the majority of studies did not identify HRV species. Jenkins et al. reported that HRV-C infections were associated with more severe sinus symptoms which is similar to findings seen in asthma [8].

In summary, the viruses that are frequently associated with CRS are rhinovirus, respiratory syncytial virus, parainfluenza virus, and influenza virus. Other viruses, such as adenovirus did not show a strong correlation to CRS populations compared to controls. The coronavirus disease of 2019 (COVID-19) pandemic has also brought an increased focus to viruses in sinonasal disease. Severe acute respiratory syndrome
(SARS)-Coronavirus 2 (SARS-CoV-2), is the etiologic virus responsible for COVID-19, and its receptor angiotensin-converting enzyme 2 (ACE2) is highly expressed in the nasal and sinus epithelia [9]. RNA viruses and respiratory diseases can increase ACE2 expression. RV and subtypes RV-A and RV-C significantly upregulate ACE2 expression, including the truncated isoform deltaACE2 (dACE2) in human nasal airway epithelial cells [10][11]. Similar symptoms such as olfactory dysfunction are found between SARS-CoV-2 and CRS, but no conclusive results were discovered on whether patients with SARS-CoV-2 have an increased risk of CRS [12][13].

**Virus receptors and targets in the upper airway**

There are several known viruses associated with CRS and it is important to analyze and study the mechanisms of infection as well as the specific receptors each virus targets. These RNA viruses reviewed include rhinovirus (RV), influenza virus, RSV and Parainfluenza virus (PIV) (Table 2) [14].

RV and its subtypes invade the host cells using three types of cellular membrane glycoproteins which include: intercellular adhesion molecule 1 (ICAM-1), low density lipoprotein receptor (LDLR) family members, and cadherin-related family member 3 (CDHR3) [15-18]. The ICAM-1 receptor is located in the plasma membrane and cytoplasm on the apicolateral portions of the airway epithelial cells. ICAM-1 mediates leukocyte adhesion and regulates endothelial cell shape as well as blood vessel barrier function [19]. When expressed by dendritic or natural killer cells, ICAM-1 plays a significant immunological role in T-lymphocyte binding and forming immune synapses. A more recently discovered role of ICAM-1 is promoting macrophage efferocytosis, or
the removal of dying cells, which is important for resolving inflammation and tissue homeostasis [19][20]. In the presence of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and interferon gamma (IFN-γ), ICAM-1 expression increases while glucocorticoids further inhibit its expression. ICAM-1 activates transcription factors, increases cytokine production, and is used by a majority of RV-A and all of RV-B subgroups [15][21][22]. The LDLR family members comprise a group of endocytic cell surface receptors which bind to extracellular ligands (e.g. lipoproteins, exotoxins, and lipid-carrier complexes) and bring them into the cell. These receptors mediate lipoprotein ligands including chylomicron, low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), or very low-density lipoprotein (VLDL). LDLR proteins normally play a significant role in cardiovascular disease and lipoprotein homeostasis as well as atherosclerosis [23]. They are located in recycling endosomes, or less commonly, the plasma membrane, and they target 12 known RV-A types [15][23]. The family of cadherins are a group of transmembrane glycoproteins whose functions include adhesion, cell signaling, and mechanical transduction. CDHR3 receptors are highly expressed in airway epithelium and are located in the plasma membrane. The CDHR3 receptor was found to be strongly associated with asthma exacerbations in children and mediates virus binding and replication for the subgroup RV-C [15][24][25].

Influenza virus contains a viral attachment protein called hemagglutinin (HA) that is a naturally occurring glycoprotein causing agglutination of red blood cells. HA in influenza virus binds to and utilizes sialic acid-containing molecules as receptors to gain entry into the cell. This leads to infection of multiple cell types utilizing these abundant
molecules as receptors, resulting in virus binding to nonproductive sialic acid-containing molecules. Therefore, the influenza virus also contains a second viral surface protein, neuraminidase, that can cleave sialic acid to release the virus after binding to any molecules that do not lead to viral infection. Influenza virus primarily targets airway epithelial cells using α2,6-type receptors in humans [26].

RSV targets ciliated epithelial cells in the airways in which the RSV-fusion (RSV-F) glycoprotein binds to the cellular receptor human nucleolin (NCL). However, it has been suggested that RSV also uses signaling receptors that activate kinases and mediate its entry. Griffiths et al. found that the insulin-like growth factor1 receptor (IGF1R) inhibitor PQ401 and a polyclonal anti-IGF1R antibody reduced infection by equivalent amounts, and that insulin-like growth factor (IGF)-1 enhanced RSV infection significantly. There was also colocalization of IGF1R with RSV particles in cells that suggested RSV interaction with IGF1R during virus entry [27]. Anderson et al. found that the human chemokine receptor, C-X3-C Motif Chemokine Receptor 1 (CX3CR1), may be a receptor for RSV infection as RSV viral loads were greatest in cells that expressed CX3CR1. Meanwhile, blocking the interaction resulted in reduced levels of RSV viral loads [28].

Human parainfluenza viruses have three types of receptors, high-power field (HPF) 1, 2, and 3, where each type targets different areas of the respiratory tract. HPF3 targets the upper respiratory tract leading to respiratory diseases like bronchiolitis and pneumonia. Similar to influenza virus, the receptor binding hemagglutinin-neuraminidase (HN) interacts with sialic acid-containing molecules on the cell surface for HPF3 mediated membrane fusion as well as using the HPF3 fusion protein [29].
Immunologic responses to viruses

There are two main immune responses to viral infection. Type 1 immune responses (Th1) are characterized by the production of cytokines that exhibit pro-inflammatory responses such as interferons (IFN). Type 2 immune responses (Th2) are characterized by eosinophilic and immunoglobulin E (IgE) responses as well as interleukins (i.e IL-10, IL-4, IL-13 and IL-5). These responses are associated with atopy and are anti-inflammatory. In a healthy immune system, Th1 and Th2 responses balance each other and lead to an optimal immune response [30]. However, a dysregulated immune response to viral infections can result in the activation of airway remodeling, epithelial-mesenchymal transitions, and epithelial barrier breakdown that are central to the pathogenesis of CRS [31].

RV infection occurs at the airway epithelium and activates Toll-like receptor 7 (TLR7) and retinoic acid-inducible gene I (RIG-1) triggers to induce cytokine expression of type I and type III interferons. Interferons are classified based on amino acid sequence and structure. Type I IFNs bind and signal through the interferon alpha and beta receptor subunit (IFNAR)-1 and IFNAR2 receptor complex, while type III IFNs signal through IFNAR1 and IL-10R2 receptors [32-34]. Both type I and type III IFNs use the same Janus kinases (JAKs) that initiate IFN-mediated signaling cascades for signal transduction, but structurally, type I IFNs have longer and straighter α-helices than type III IFNs. and type III IFNs closely resemble the structure of IL-22 from the IL-10 family of cytokines [35-39]. Using human nasal epithelial cells (hNEC), Tan et al. discovered that RV infection induced the expression of C-X-C Motif Chemokine Ligand (CXCL)-9,
CXCL11, interferon γ-induced protein 10 (IP-10), and Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES), which are all type 1 immune responses. Although cytokine and chemokine expression were dominated by type 1 immune responses, moderate expression of type 2 immunity genes were also discovered [40]. In a study by Kim et al., researchers found that cytokines induced by RV were the same between patients with CRS and patients without CRS. However, there was a slight impairment of Interferon-β (IFN-β) protein production and a delay of Melanoma Differentiation-Associated protein 5 (MDA5) mRNA expression [41]. Other studies have found that RV-B releases less proinflammatory cytokines, chemokines, and interferons than the other subtypes of rhinovirus: RV-A and RV-C [42]. In a study by Yeo et al. researchers found that rhinovirus infection resulted in significantly decreased mRNA levels of tight junction components such as Zonula occludens-1 (ZO-1), occludin, claudin-1, as well as adherens junction components like cadherin-1 in epithelial cells (Table 2) [43]. Epithelial cells act as a barrier and the first line of defense against infections. Therefore, loss of barrier function via degraded tight junction and adherens junction components can result in increased risk for chronic infection due to microbes and antigens being more likely to pass through the defective barrier [44].

RSV infections are one of the most common causes of respiratory infections in children and infants. Most studies detailing the immune response due to RSV used patients who had lower respiratory tract infections. In patients infected with RSV, IFN-γ levels were shown to be increased in both the nasal mucosa and the lungs. Additionally, in patients with lower IFN-γ production there were increased severity scores [45-48]. In terms of Th2-response, there were increased levels of IL-4, IL-6, IL-9, IL-10, and IL-13
found in the nasal washes of RSV infected children [45][49][50]. According to data from one study, a predominance from Th2 cytokines over Th1 cytokines was associated with children with hypoxic RSV lower respiratory tract infection (RSV LRTI), suggesting that a Th2-biased response is associated with severe manifestations of RSV infection [45]. Interestingly, several studies on RSV have shown that its pathogenesis is dependent on age. Using mice models, Hijano et al. found that type I interferons, such as interferon-alpha (IFN-α), were differentially expressed based on age. Conversely, IL-33, a Th2 oriented cytokine, was released in large amounts following RSV infections in neonatal mice, but the response decreased in adult mice [51]. Results from a study by Saravia et al. confirmed these results, finding that neonatal mice that were induced with RSV responded with high levels of IL-33 expression and significant increases in type 2 innate lymphoid cells (ILC2), while adult mice failed to induce either. This study also found that amongst infants hospitalized with RSV infections, IL-33 and IL-13 levels were elevated (Table 2) [51].

Parainfluenza viruses primarily affect children and are associated with the induction of wheezing early in life. In a study by Yoshizumi et al., researchers determined that cells infected with PIV released greater amounts of IL-1β, IL-6, TNF-α, IL-1ra, IFN-γ, IL-2, IL-4, IL-5, IL-10, G-CSF, GM-CSF, IL-8, IP-10, eotaxin, RANTES, pallet derived growth factor (PDGF) bb, and vascular endothelial growth factor (VEGF) when compared to cells with no PIV (Table 2) [53].

Studies have shown that patients infected with influenza A virus have increased levels of IL-6, IL-8, TNF-α, IL-10, and IFN-γ in their nasal lavage samples (Table 2). These cytokines also correlate with disease severity- as levels increased, disease
severity increased [54]. According to a study by Skoner et al., IL-6 was determined to have a potential role in initiating symptoms of influenza A infection while IL-8 did not [55].

As these upper respiratory viruses infect the epithelium, they trigger immune responses which induce the release of cytokines and chemokines via intracellular sensors TLR7 and retinoic acid-inducible gene I (RIG-I). Cytokines and chemokines, such as interleukin 6 or interferon-γ (IFN-γ), are induced and secreted by the intracellular sensors before recruiting neutrophils and macrophages that activate the Th1 immune response [32-34][53,54]. The immune response leads to inflammation in the infected areas which coupled with the damage from the viral infection itself and from the viral elimination by lymphocytes (e.g., Th1 cells, cytotoxic T cells), results in damage to the epithelium [90]. Continuous viral infection and inflammation cause airway remodeling of the nasal epithelium and degradation of tight junctions (TJs) and adherens junctions (AJs) [43,44]. Disrupted mechanical barriers and deficiencies in both the innate and acquired immune system make the sinonasal mucosa more susceptible to antigenic exposition and stimulation, leading to either side of the spectrum of chronic inflammation. This results in increased viral susceptibility of the epithelium allowing further disease exacerbations and greater potential for bacterial infections to occur. As the epithelium becomes degraded, the persistent infections and immune responses lead to CRS and CRS exacerbations [88]. Epithelial damage has been observed in CRSwNP, and genetic deficiency or environmentally induced damage in epithelial repair mechanisms may be associated with both forms of CRS [86][87][89].
Risk factors for viral infections in CRS

There are several risk factors that can contribute to viral binding, entry, replication, and immune response that may contribute to CRS infections. Epithelial barriers are critical in preventing viral binding and entry into sinonasal epithelia. Mutations in CDHR3, the primary viral receptor for RV-C, have been associated with an increased risk for CRS and asthma [24]. One hypothesis is that the rs6963770 single nucleotide polymorphism (SNP) may result in increased RV-C binding and modulate a dysregulated immune response [56]. Age is considered a risk factor for RSV infection, as we see high rates of the serious infection and hospitalization amongst infants. Additionally, the presence of underlying conditions such as prematurity, congenital heart disease, immunosuppression, and cystic fibrosis all increase the risk of developing severe RSV infections [57]. Similar to RSV, PIV infections are common and tend to be more severe in infants and young children, or elderly with compromised immune systems [58]. For influenza, a study of children in Ontario, Canada found that asthma, regardless of the severity, was a significant risk factor associated with severe disease [59].

Allergic rhinitis and asthma are highly co-expressed with CRS suggesting a common mechanism of disease. In all three of these type 2-mediated airway disorders, the epithelial barrier is compromised. This leakiness in the epithelial barrier is hypothesized to allow enhanced viral entry through the epithelia to trigger alarmin signals including thymic stromal lymphopoietin (TSLP), IL-33, and IL-13 which can trigger type 2 activation of mast cells and eosinophils. Similar mechanisms of epithelial
barrier dysfunction can be seen in prolonged exposure to tobacco and air pollution which are highly associated with CRS risk [60-63].

Aside from risk factors pertaining to an increase in CRS risk, there are risk factors for acute CRS exacerbations that increase nasal and sinus symptom severity. General health risk factors include smoking, a higher body-mass index (BMI), previous sinus surgeries and a longer CRS status, while several seasonal components like hay fever or winter seasons also contribute to increasing acute CRS exacerbation risk [50]. Comorbid predisposing factors include asthma symptoms, impaired mucociliary clearance, or atrophic rhinitis [64-66].

**CRS related viruses in Children vs Adults:**

Age is a strong risk factor for CRS. Children have 3-8 viral URIs per year compared to adults who only have 2-4 URIs [67]. Male children under the age of 3 more commonly contract respiratory illnesses compared to female children of similar age while the opposite is true as their ages progress [68][69]. Comorbid conditions like allergic rhinitis were found in 36-60% of pediatric patients with CRS [70-72]. Khoo et al. found that asthma and wheezing exacerbations in children were more prevalent the younger the age. RV-C was the most frequently identified viral pathogen in these children and several viruses including RSV, PIV, and influenza were also detected [73].

Certain viruses are more predominant in certain age groups. Interestingly, studies examined in this review revealed that RSV and PIV are notably more prevalent in certain age groups. For example, children and the elderly are well documented as being more susceptible to RSV infection than adolescents or adults. Immature immune
systems or low lymphocyte counts in infants and young children, as well as low-levels of RSV-neutralizing antibodies in patients over 65 are factors that cause these age groups to be more susceptible to infection [74][75]. Furthermore, RSV pathogenesis differs in children and adults. For example, most adults and elderly infected with RSV show symptoms similar to influenza infection, while infants and young children with RSV infections often progress to lower respiratory tract infections (LRTI) and wheezing [76-78]. Additionally, PIV infection often causes URTIs in most healthy young adults, but more frequently leads to severe symptoms and lower respiratory illnesses in young children. Similarly to RSV, PIV infection is one of the leading causes of acute respiratory tract infections in young children under the age of five, accounting for approximately 17% of hospitalizations [58][79-80].

Conclusion

In summary, CRS affects millions of people worldwide and poses a significant financial burden. Therefore, understanding the mechanisms of infection that drive its pathology is important. In order to devise effective therapies for patients with CRS, understanding the viruses, their mechanisms of infections, and their immune responses is crucial. Rhinovirus is a frequently isolated virus in patients with CRS. RSV, PIV, and influenza virus are also isolated in patients with CRS. These four viruses have many similarities such as targeting epithelial airway cells and being RNA viruses. However, prevalence, receptor type, and immune response varies from virus to virus.

RV was the most widely and thoroughly studied virus in terms of CRS specifically, and even in terms of URI and acute sinusitis. In the future, we hope to see
more studies that detail the immune response of upper respiratory tract infections and CRS due to RSV, PIV, and influenza virus. Additionally, we hope to see more longitudinal studies that follow infants and young children infected with serious respiratory viruses and how that can contribute to the onset of more serious cases of URI, such as CRS, later in adulthood. Throughout this review, we noticed a scarcity of papers on pediatric CRS as well. Research indicates that this time point is critical in understanding the development and onset of adult CRS. These additional studies are necessary to be better able to target and create new therapies.

**Author Contributions:**

Conceptualization: all authors. Data curation: HSL, SV. Formal Analysis: all authors. Methodology: all authors. Project Administration: EHC. Writing—original draft: HSL, SV. Writing—review & editing: EHC.

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Tables:

**Table 1: URI Progression Characteristics**

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Upper Respiratory Infection (URI)</th>
<th>Acute Rhinosinusitis (ARS)</th>
<th>Chronic sinusitis (CRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
URI, the most mild form of sinus infection, lasts between 7-11 days, while ARS and CRS are more severe. ARS is considered moderate and diagnosis requires the persistence of symptoms beyond 10 days, with a failure of improvement for at least 10 days. CRS is described as severe, and is characterized by the presence of symptoms for at least 12 weeks [1][81][82][83].

Table 2: Characteristics of Viruses Associated with CRS

<table>
<thead>
<tr>
<th>Virus</th>
<th>Characteristics</th>
<th>Receptors</th>
<th>Location of Receptors</th>
<th>Immune Response &amp; Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>Most common virus isolated in patients with CRS [4].</td>
<td>ICAM-1 and LDLR for RV-A and RV-B [15][16]</td>
<td>ICAM-1 is expressed in most tissues at low levels, particularly in endothelial cells [84].</td>
<td>Induced expression of CXCL9, CXCL11, IP-10, and RANTES [40]</td>
</tr>
<tr>
<td></td>
<td>3 distinct subtypes: RV-A, RV-B, and CDHR3 for RV-C [18]</td>
<td></td>
<td></td>
<td>Degrades tight junction (TJ) and adherens junction (AJ) components [43].</td>
</tr>
<tr>
<td>Virus</td>
<td>Description</td>
<td>Receptors/Expression</td>
<td>Inflammatory Cytokines</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>RV-C</td>
<td>RV-C, with RV-C being the most severe [7].</td>
<td>α2,6-type receptors [26]</td>
<td>Increased levels of IL-6, IL-8, TNF-α, IL-10, and IFN-γ [54]</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>Causes destruction of airway epithelial cells [7].</td>
<td>Airway epithelial cells [26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>Common cause of respiratory infection in children [45].</td>
<td>NCL, IGF1R, CX3CR1 [27][28]</td>
<td>Age dependent immune response: IL-33 increased in neonatal mice, but not in adult mice [51][52].</td>
<td></td>
</tr>
<tr>
<td>PIV</td>
<td>Primarily affects young children [53].</td>
<td>Cell surface, Airway epithelial cells [29]</td>
<td>IL-1β, IL-6, TNF-α, IL-1ra, IFN-γ, IL-2, IL-4, IL-5, IL-10, G-CSF, GM-CSF, IL-8, IP-10, eotaxin, RANTES, PDGF-bb, and VEGF [53]</td>
<td></td>
</tr>
</tbody>
</table>

Despite having different receptors, these four viruses frequently isolated in CRS patients are all expressed in epithelial cells.

**Figures:**
Figure 1: As a virus infects the upper airway epithelial cells it activates TLR7 and RIG1. These receptors induce the release of type I and type III interferons, as well as IL-6 and IL-8 and other cytokines, to promote a Th1 immune response. A Th2 immune response is also induced through the production of IL-4, IL-5, IL-13 and other cytokines. The immune response creates inflammation and airway remodeling. Prolonged inflammation results in airway remodeling which contributes to CRS due to disrupted epithelial barrier function. As the epithelium is weak and damaged, viral susceptibility increases, resulting in further CRS and upper respiratory disease exacerbations. Additionally, the environment that results from this immune response also creates a suitable
environment for bacterial infection, as the epithelial barrier is weak. [32-34][53,54][87][88]. Created with BioRender.com
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<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>7-11 days (up to 14)</td>
<td>&gt;10 days</td>
<td>&gt;12 weeks</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Stuffy and runny nose, mild cough, watery eyes, sneezing, low-grade fever, yellow/green nasal discharge, headache, mild tiredness</td>
<td>Thick yellow/green mucus in the nose, facial pain and tenderness especially in the eyes, cheeks, or nose, post nasal drainage (PND), nose congestion</td>
<td>Increased facial pain, PND, reduced sense of smell or taste, nose congestion, nasal inflammation</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>yellow/green mucus</td>
<td>Thick mucus</td>
<td>Swelling and polyps</td>
</tr>
<tr>
<td>Radiology</td>
<td>Mucosal thickening &lt;4mm or absence of mucosal thickening</td>
<td>Mucosal thickening &gt;4mm, obstruction of osteomeatal complexes</td>
<td>Polyps and sinus obstruction, mucosal thickening</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive (e.g. saline nasal sprays)</td>
<td>Pain relievers, Nasal steroids, Decongestants, Antibiotics</td>
<td>Oral steroids, Functional Endoscopic Sinus Surgery, Biologic therapies</td>
</tr>
</tbody>
</table>

URI, the most mild form of sinus infection, lasts between 7-11 days, while ARS and CRS are more severe. ARS is considered moderate and diagnosis requires the persistence of symptoms beyond 10 days, with a failure of improvement for at least 10 days. CRS is described as severe, and is characterized by the presence of symptoms for at least 12 weeks [1][81][82][83].

### Table 2: Characteristics of Viruses Associated with CRS

<table>
<thead>
<tr>
<th>Virus</th>
<th>Characteristics</th>
<th>Receptors</th>
<th>Location of Receptors</th>
<th>Immune Response &amp; Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>Most common</td>
<td>ICAM-1 and</td>
<td>ICAM-1 is</td>
<td>Induced expression of</td>
</tr>
<tr>
<td>Virus</td>
<td>Causes/Distribution</td>
<td>Receptors</td>
<td>effects</td>
<td>Other</td>
</tr>
<tr>
<td>-------</td>
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<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Influenza</td>
<td>Causes destruction of airway epithelial cells [7]</td>
<td>α2,6-type receptors [26]</td>
<td>Airway epithelial cells [26]</td>
<td>Increased levels of IL-6, IL-8, TNF-α, IL-10, and IFN-γ [54]</td>
</tr>
<tr>
<td>RSV</td>
<td>Common cause of respiratory infection in children [45].</td>
<td>NCL, IGF1R, CX3CR1 [27][28]</td>
<td>IGF1R can be expressed in lung epithelium. [27]</td>
<td>Age dependent immune response: IL-33 increased in neonatal mice, but not in adult mice [51][52].</td>
</tr>
<tr>
<td>PIV</td>
<td>Primarily affects young children [53].</td>
<td>Interaction between HN and sialic acid-containing receptor on cell surfaces: α2-3-linked SAs, and α2-8-linked SAs [29][85]</td>
<td>Cell surface, Airway epithelial cells [29]</td>
<td>IL-1β, IL-6, TNF-α, IL-1ra, IFN-γ, IL-2, IL-4, IL-5, IL-10, G-CSF, GM-CSF, IL-8, IP-10, eotaxin, RANTES, PDGF-bb, and VEGF [53]</td>
</tr>
</tbody>
</table>

Despite having different receptors, these four viruses frequently isolated in CRS patients are all expressed in epithelial cells.
Figure 1: Viral Infection to CRS Pathogenesis

Nasal Epithelium

- TLR7, RIG1 activation
  - IL-4, IL-5, IL-13 upregulation
  - IFN-β and IFN-γ, IL-6, IL-8 upregulation

- Th1 and Th2 immune response and inflammation

Damage to epithelium

- Airway remodeling and increased viral infections
- Increased virus susceptibility and further disease exacerbations

Airway remodeling and increased viral infections leads to more susceptible to bacterial infection due to degraded epithelial barrier.