*Review article*

# Viral infections and chronic rhinosinusitis

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**Viral infections are the most common cause of upper respiratory infections; they frequently infect adults once or twice and children 6 to 8 times annually. In most cases, these infections are self-limiting and resolve. However, many patients with chronic rhinosinusitis (CRS) relay that their initiating event began with an upper respiratory infection that progressed in both symptom severity and duration. Viruses bind to sinonasal epithelia through specific receptors, thereby entering cells and replicating within them. Viral infections stimulate interferon-mediated innate immune responses. Recent studies suggest that viral infections may also induce type 2 immune responses and stimulate the aberrant production of cytokines that can result in loss of barrier function, which is a hallmark in CRS. The main purpose of this review will be to highlight common viruses and their associated binding receptors and highlight pathophysiologic mechanisms associated with alterations in mucociliary clearance, epithelial barrier function, and dysfunctional immune responses that might lead to a further understanding of the pathogenesis of CRS. (J Allergy Clin Immunol 2023;■■■:■■■-■■■.)**

***Key words:*** *Chronic rhinosinusitis, upper respiratory tract infection, airway epithelium, innate immunity, genetics, virus, barrier function*

*Abbreviations used*

| | |
|---|---|
| ACE2: | Angiotensin-converting enzyme 2 |
| CDHR3: | Cadherin related family member 3 |
| COVID-19: | Coronavirus disease 2019 |
| CRS: | Chronic rhinosinusitis |
| ICAM-1: | Intracellular adhesion molecule 1 |
| IRF: | Interferon regulator factor |
| RSV: | Respiratory syncytial virus |
| RV: | Rhinovirus |
| SARS-CoV: | Beta-coronavirus responsible for severe acute respiratory syndrome |
| SARS-CoV-2: | Beta-coronavirus responsible for COVID-19 |
| SNP: | Single-nucleotide polymorphism |
| TER: | Transepithelial resistance |
| TJ: | Tight junction |
| TRIF: | TIR-domain-containing adapter-inducing interferon-β |
| URI: | Upper respiratory infection |
| ZO-1: | Zona occludens-1 |

Upper respiratory infections (URIs) are among the most common medical diagnoses in the United States, with costs exceeding $22 billion annually.[1] The majority of URIs are due to human rhinovirus (RV), respiratory syncytial virus (RSV), influenza, and human coronavirus infections.[2,3] These viruses bind to receptors in the nasal airway that mediate cell entry, thereby allowing viral replication, which triggers an interferon antiviral host immune response. This inflammatory response can manifest with symptoms of fever, nasal congestion, hyposmia (decrease in smell), facial pain and/or pressure, and postnasal drainage. In most cases, this immune response is self-limiting and returns to a homeostatic baseline after the viral infection is cleared. However, an aberrant host immune response after viral infections characterized by chronic inflammation, decreased mucociliary clearance, and loss of the epithelial barrier function may be 1 hypothesis for the development of chronic rhinosinusitis (CRS).[4,5] This hypothesis is supported by a longitudinal study in which recurrent colds in childhood were identified as a significant risk factor for the development of sinusitis in children and in adults.[6]

In this review, we highlight common respiratory viruses associated with sinusitis and their potential role in the development of CRS. We discuss the role of the host immune response to viruses and how dysregulation might contribute to chronic inflammation and loss of the protective airway barrier. We also discuss the role of virus subtypes and genetic risk factors that might contribute to the pathogenesis of CRS.

## VIRAL SUBTYPES AND CLINICAL DISEASE

Not all virus subtypes within each family have similar clinical effects. For example, RV infections are the most common cause of URIs[7]; they have also been linked to CRS and sinusitis exacerbations.[4] HRVs, which are positive-strand RNA viruses in the family Picornaviridae, are divided into 3 species: HRV-A, HRV-B, and HRV-C. HRV-A and HRV-B species were identified and sequenced in the 1980s; however, HRV-C was not identified until 2006, as it did not grow in standard viral media.[8] The advent of viral sequencing and subsequent distinctions of RV species have revealed that HRV-A and HRV-C sinus infections result in more severe symptoms than HRV-B does.[9] This epidemiologic finding is supported by *in vitro* and *in vivo* findings that reveal a heightened immune response, as measured by gene expression and cytokine signals, after HRV-A and HRV-C infections versus the response to HRV-B infections.[9,10]

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RSV is the second most common virus identified in sinus infections; it consists of 2 subtypes, RSV-A and RSV-B, which differ in terms of antigen sequences.[11] In most epidemiologic studies, RSV-A tends to be the predominant virus identified in children, and compared with RSV-B, RSV-A tends to have a more severe response and require intensive care unit admission in children secondary to bronchiolitis.[12-14] More significant than virus subtype is patient age. Although RSV can infect people of all ages, infants, children, and elderly individuals are at a significantly higher risk of lower airway morbidity and mortality owing to impaired antiviral host responses.

Influenza viruses are negative-sense single-strand RNA viruses from the family Orthomyxoviridae. Although there are 4 types of influenza viruses (A, B, C, and D), only influenza A and B cause seasonal flu infections in humans.[15,16] Influenza subtypes are based on the combinations of the hemagglutinin and neuraminidase proteins on the surface of the virus. Influenza A tends to produce more symptoms and is the only subtype known to cause epidemics. In 2009, the influenza A subtype H1N1 was declared a pandemic,[17] with cases of severe acute respiratory distress and death reported in high-risk populations, including the morbidly obese and pregnant patients.[18]

Human coronaviruses are enveloped positive-sense RNA viruses from the family Coronaviridae. The common viral strains of human coronavirus, namely, 229E (alpha-coronavirus), NL63 (alpha-coronavirus), OC43 (coronavirus), and HKU1 (beta-coronavirus), typically cause only mild symptoms. However, there are more severe strains, including the beta-coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), the beta-coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), and the beta-coronavirus responsible for coronavirus disease 2019 (COVID-19) (SARS-CoV-2), which cause high rates of morbidity and mortality.[19]

## VIRUS RECEPTORS AND BINDING

Respiratory viruses are transmitted via mucosal surfaces in either the nasal or oral cavities. In the nasal airway, fusion proteins on the virus envelope bind to nasal epithelial cells through specific receptors present on the cell surface. This triggers translocation, in which the RNA virus can then enter the epithelial cell and replicate via the host cell machinery. These viruses are then shed by the cell and can infect other host cells. Virus subtypes, their receptors, and their associated clinical symptoms are highlighted in Table I.

There are 3 different receptors for RV infections. Intracellular adhesion molecule 1 (ICAM-1) is a cell surface glycoprotein that mediates leukocyte adhesion in endothelial cells and cell migration, barrier function, and proliferation in epithelial cells.[20] RV-A and RV-B, which together constitute the major group of RV serotypes (90%), use ICAM-1 as their receptor,[21,22] whereas the minor group of RV serotypes (10%) use low-density lipoprotein receptor (LDLR) as their receptor.[23] In 2014, Bonnelykke et al determined that a missense variant in the rs6967330 single-nucleotide polymorphism (SNP) resulting in a cysteine-to-tyrosine substation was highly associated with severe childhood asthma exacerbations.[24] Further analysis of this SNP revealed that it was associated with differential expression of the cadherin related family member 3 gene (*CDHR3*) in 2015. CDHR3 is a transmembrane protein that is highly expressed at the cell surface during mucociliary differentiation. Bochkov et al, in an elegant study using differentiated sinonasal airway epithelial cells, found that CDHR3 was a receptor for HRV-C.[25] Subsequent studies by Basnet et al suggest that cells expressing the rs6967330 SNP have increased binding and replication of HRV-C.[26] This genetic risk factor may explain why, in a multicenter study, persons with the rs6967330 SNP had 2-fold increased odds of having adult CRS.[27]

RSV enters cells by binding the G protein attachment to either heparin sulfate proteoglycans or CX3CR1 receptors present on airway cells.[28,29] This binding then allows the RSV F protein attachment to bind to nucleolin (NCL), insulin-like growth factor-1 receptor (IGF1R), epidermal growth factor (EGFR), and ICAM-1 and enter the cell.[30] Susceptibility to RSV has been associated with SNPs in genes regulating innate immune host responses, including the vitamin D receptor *JUN*, a gene involved in proinflammatory cytokine production, and *IFNA5*, an interferon gene.[31]

Influenza uses the hemagglutinin protein on its cell surface to bind to sialic acid–containing receptors on airway cells and other cell types.[32] Influenza virus typically enters the human body through the upper respiratory tract, causing sinusitis symptoms. However, the virus can spread to the lower respiratory tract, which can lead to life-threatening illnesses secondary to uncontrolled cytokine production. Chatzopoulou et al assessed complement-related genetic risk factors in more than 200 individuals during the 2009 H1N1 influenza pandemic who were grouped according to disease severity. Chatzopoulou et al discovered that persons with SNPs in the *CD55* gene (rs2564978) and in the *C1QBP* gene (rs3786054) were associated with increased mortality but not disease severity.[33]

Different strains of human coronavirus bind to epithelial cells via different receptors. For example, the common human coronavirus HCoV-229E is a pathogen that is frequently responsible for URI disease and uses human aminopeptidase N (APN) as its entry receptor to invade cells.[34] Alternatively, both SARS-CoV and SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2) to enter cells. ACE2 is expressed on the apical surface of epithelial cells in the lung and nasal airways.[35] Attachment of the virus to the host cell membrane is mediated by the S glycoprotein on the viral surface.[36] The S protein on SARS-CoV strains is split into 2 subunits: the S1 subunit binds ACE2, whereas the S2 subunit anchors the S protein to the membrane.[37] Ziegler et al recently determined that *ACE2* was an interferon-stimulated gene,[38] and our laboratory reported that RV infections in asthmatic individuals increased ACE2 expression.[39] This finding suggests that common viral infections, including RV, RSV, and influenza, might increase ACE2 expression and COVID-19 disease severity.

## HOST IMMUNE RESPONSE (INTERFERONS)

Viruses can activate the immune system via different mechanisms. The immediate immune response is via the innate immune system; it is designed to block or inhibit viral infection, protect host cells, and kill virus-infected cells. The innate immune system is initiated by activation of pattern recognition receptors in the host cell. Viral RNA can activate Toll-like receptors (TLRs) on the cell surface,[40] and/or cytoplasmic receptors, including retinoic acid-inducible gene I (RIG-I), or melanoma differentiation-associated gene 5 (MDA-5), can be activated within the cell. These pattern recognition receptors can then activate signal integrators such as myeloid differentiation factor 88 (MyD88), TIR domain–containing adapter-inducing IFN-β

**TABLE I.** Virus subtypes, surface receptors, and clinical disease

| Virus | Subtypes | Surface receptors | Clinical disease |
|---|---|---|---|
| RV | RV-A | ICAM-1, LDLR | Associated with more severe sinus symptoms |
| | RV-B | ICAM-1, LDLR | Associated with milder sinus symptoms |
| | RV-C | CDHR3 | Associated with more severe sinus symptoms and exacerbations of childhood asthma |
| RSV | RSV-A and RSV-B | RSV G protein binds CX3CR1 and HSPG; RSV F protein can interact with NCL, EGFR, IGF1R, and ICAM-1 | Frequent cause of wheezing and severe bronchiolitis in infants and young children. Associated with URIs and LRTIs. Increased morbidity in infants and young children. RSV-A is more common in children and associated with a higher severity of illness than RSV-B |
| Influenza | Influenza A and B | Sialic acid–containing receptors on airway cells, α(2,6)-linked sialic acid receptors in humans | Common presenting signs include fever, cough, rhinorrhea, and vomiting. Influenza A is associated with more severe symptoms, and its rapid spread can be associated with epidemic/pandemics. Severe acute respiratory distress and death have been reported in high-risk populations |
| Coronavirus | HCoV-229E | Human aminopeptidase N | Mild URI symptoms, within the range of those of typical common colds |
| | SARS-CoV | S glycoprotein attachment to ACE2 | Virus responsible for SARS. Highly contagious; it may present initially as fever, myalgia, and headache and progress to cough, dyspnea, and respiratory distress |
| | SARS-CoV-2 | S glycoprotein attachment to ACE2 | Virus responsible for COVID-19. Highly contagious, with symptoms ranging from mild URI symptoms, hyposmia/anosmia; it can progress to severe lower respiratory symptoms with high rates of morbidity and mortality |

*EGFR,* Epidermal growth factor; *HCoV*, human coronavirus; *HSPG*, heparin sulfate proteoglycan; *IGF1R*, insulin-like growth factor-1 receptor; *LDLR*, low-density lipoprotein receptor; *LTRI*, lower respitoratory tract infection; *NCL*, nucleolin.

(TRIF), nuclear factor-κB (NF-κB), and interferon regulator factor (IRF) transcription factors.[41] Activation of these signal integrators promotes expression of antiviral interferons, interferon-stimulated genes, and inflammatory cytokines.[42]

Interferons are a family of cytokines that interfere with virus replication; they can be divided into 3 groups. Type 1 interferons are the most studied antiviral cytokines; they include IFN-α and IFN-β. Type 1 interferons can directly inhibit virus replication and stimulate adaptive immune responses of B cells to produce antibodies and T cells to recognize and destroy virus-infected cells. Type 2 interferons (IFN-γ) can orchestrate macrophage, neutrophil, dendritic cell, and natural killer cell responses. Type 3 interferons (IFNλ and IL-10) can mediate antiviral responses.[43] Although interferon responses are critical for antiviral innate immunity, there is evidence that prolonged and sustained interferon production may also contribute to chronic inflammation.[44]

There have been several *in vivo* and *in vitro* studies of host innate immune response to RV in sinusitis; these studies have yielded conflicting results. Tan et al were among the first groups to use air-liquid interface cultures that replicated nasal epithelia to assess the immunologic response to RV infection. They found that RV infection induced CXCL-11, IP-10, CXCL-9, and RANTES expression and activated Toll-like receptor 7 (TLR7) and retinoic acid–inducible gene 1 (*RIG-1*) pattern recognition signaling cascades to induce type 1 and 3 interferon signaling pathways.[45] Kim et al assessed epithelial immune responses to RV in ALI cultures from controls and patients with CRS. They found that although antiviral cytokine production in cultures from patients with CRS was no different from that in healthy controls, there was a slight reduction in IFN-β and MDA5 mRNA expression, which might result in decreased clearance of virus.[46] Lee et al, in a similar *in vitro* study, found that RV-induced production of antiviral interferon responses was no different between samples from controls and patients with CRS with nasal polyp tissues.[47] Hwang et al then compared type 1 and type 3 interferon responses to respiratory viruses in the nasal tissues of healthy controls and patients with CRS. They found that type 1 and type 3 interferon responses were significantly decreased in patients with CRS versus in controls.[48] One possible explanation for these findings might be related to timing. In studies of viral responses in asthma, asthmatic individuals were found to have interferon impairment at baseline, resulting in enhanced RV replication. This resulted in higher viral loads that then upregulated antiviral signals, thereby resulting in an exaggerated interferon response later during asthma exacerbation.[49] This hypothesis is supported by *in vivo* changes in host response after CRS exacerbations, which were characterized by significantly increased levels of IL-6, major basic protein, and myeloperoxidase in nasal lavage fluids versus at baseline and in healthy controls.[50,51]

The host immune response to RSV infection differs depending on the age of the patient. In infants, the very low IFN-λ response in nasal fluids is related to a higher degree of symptoms and disease severity, including nasal congestion, sinusitis, and productive cough.[52] However, in adults, RSV infection induces increased levels of IFN-β, IFN-λ1, and IFN-γ in nasal fluid.[53] This age-related finding suggest that an immature interferon response in infants might be related to an increase in RSV symptoms.

The role of interferons as protective against influenza infection was reported by Klinkhammer et al, who used murine models.[54] In their study, both IFN-α and IFN-γ protected against the spread of influenza virus infection from the upper airway to the lungs and inhibited viral transmission from infected individuals to healthy individuals.[54] However, other studies have reported that IFN-γ is involved in the pathogenesis of influenza virus.[55,56] These studies showed that deficiency of IFN-γ signaling protected

mice with upper airway infection against development of disease severity and improved survival.[55,56] The success of the influenza virus in reducing the morbidity and mortality of flu-related disease suggests that priming the immune system to develop antibodies to circulating influenza subtypes can reduce the severity of disease.

Several studies have suggested that early antiviral immune responses in the upper respiratory tract may serve as an early indicator of disease severity in SARS-CoV-2–infected individuals.[57] In particular, interferons have been shown to have an inverse relationship with the severity of COVID-19. Weakened interferon responses in the upper respiratory airway and impaired levels of type I and type III interferons in the blood have been correlated with severe symptoms of COVID-19.[57-59] Zhang et al hypothesized that the decreased antiviral immunity seen in cultures from patients with noneosinophilic CRS might result in increased SARS-CoV2 binding and replication versus that in healthy controls.[60] Lei et al reported that IFN-β treatment effectively inhibits SARS-CoV-2 replication and that SARS-CoV-2 evades type 1 interferon production and signaling, indicating that interferons are targeted by SARS-CoV-2 to disrupt host immune response for their replication.[61,62] These findings suggest that type I and type III interferons may be potential therapies for COVID-19, and in fact, many clinical trials utilizing interferons as therapeutic agents are under way[63]; among these is a recent phase 3 trial reporting that the rate of COVID-19–related hospitalization or death was reduced by 47% in the group receiving a single dose of pegylated IFN-λ versus in the placebo group.[64]

## T-CELL–MEDIATED RESPONSES

T-cell–mediated adaptive immune responses are critical in recognizing and destroying virus-infected cells. Type 1 immune responses, which are characterized by IFN-γ and produced by $T_H1$ cells, help to protect against intracellular pathogens such as viruses. Type 2 immune responses, which are characterized by the production of IL-4, IL-5, and IL-13, are characteristic of allergic responses. Type 3 immune responses, which are characterized by $T_H17$ cells and the production of IL-17 and IL-22, are characteristic of antimicrobial responses. Classically, type 1 immune responses are the best studied of the antiviral responses; however, there is increasing evidence that type 2 and type 3 immune responses are instrumental.

Jackson et al sought to answer the question of how RV infections, which have classically triggered $T_H1$ cell IFN-γ antiviral responses, might induce $T_H2$ cell immune responses.[65] Jackson et al found that RV infections in both *in vitro* and *in vivo* models stimulated the production of IL-33, which in turn induced the secretion of the type 2 cytokines IL-4, IL-5, and IL-13.[65] Bosco et al sampled the noses of children presenting to the ER with RV-induced asthma and/or wheeze.[66,67] They found that children with a high $T_H1$ cell interferon response had mild symptoms, whereas those children with a low IFN-γ response but upregulation of EGF, IL-4, IL-6, IL-10, and TGF-β had more severe symptoms. Using gene network reconstruction, they identified IRF7 as the hub connecting interferon-mediated antiviral response.[67] When IRF7 was knocked down in airway epithelial cells, RV-induced antiviral responses were reduced and IL-33 $T_H2$ cell responses were increased, suggesting a role of interferons and IRF7 in regulating $T_H1$ and $T_H2$ cell immune responses.[68] This $T_H2$ shift in more severe RV-related airway disease might explain why the use of omalizumab, an IgE blocker, improved IFN-α responses to RV and reduced asthma exacerbations in inner-city youth.[69] It will be interesting to see whether the use of biologics targeting type 2 pathways reduces viral-mediated CRS exacerbations in the future.

Zhang et al reported that the level of IL-33, an alarmin cytokine that triggers type 2 immunity, was elevated in nasal aspirates from infants with severe RSV infection. Furthermore, blocking IL-33 has been shown to effectively inhibit RSV-induced immunopathogenesis in several respiratory animal studies,[70-72] suggesting IL-33 as a potential therapeutic target to treat airway RSV infection. Recently, a phase 3 trial of an RSV vaccine showed significant reductions in RSV-related respiratory infections and severity in older adults. Further studies assessing the host response in those who receive the RSV vaccine might shed light on whether the type 2 immune response is decreased.[73]

Type 2 inflammation and interferon production have also been shown to increase ACE2 expression in the airway epithelia, suggesting an increased risk for COVID-19 viral infections.[38,74-77] Although there are very limited data for COVID-19 infection and CRS risk, Lee et al did determine that persons with CRS in a Korean cohort had a higher risk for SARS-CoV-2 infection and severe COVID-19.[78] Interestingly, this finding was unique to patients with CRS without nasal polyps, which is classically a $T_H1$ cell–mediated disorder.

## MUCOCILIARY FUNCTION

Mucociliary clearance is a primary innate defense in the upper and lower airways. Pathogens, including viruses, are trapped in the mucus layer and then removed from the airways by motile cilia. Viruses can target this mucociliary defense through various mechanisms. CDHR3, the receptor for RV-C, is expressed exclusively on ciliated airway cells.[79] Similarly, the ACE2 receptor, which binds SARS-CoV and SARS-CoV-2, is highly expressed in ciliated airway cells, which might explain why these viruses preferentially bind to nasal airway epithelia.[80,81] For RSV infections, viral entry into the cell is mediated by 2 surface glycoproteins that bind to the CX3CR1 receptor expressed on motile cilia.[82] Viral infections can also increase the expression of mucin proteins, including MUC5AC and MUC5B, which can result in increased mucus production, thereby slowing mucociliary clearance.[83-86] Finally, SARS-CoV and SARS-CoV-2 have been shown to destroy motile cilia, possibly because of downregulation of FOXJ1, a transcription factor necessary for ciliogenesis. The end result of decreased mucociliary clearance after viral infections might promote viral spread and increase disease severity.[81]

## EPITHELIAL BARRIER FUNCTION

An intact barrier of the airway epithelium provides a physical barrier against inhaled viruses in the nose. This epithelial barrier comprises tight junction (TJ), including Zona occludens-1 (ZO-1), occludins, and claudins that mediate paracellular transport and adherens junctions, including the cadherin and catenin families, which provide cell-cell adhesion and cellular integrity by associating with the actin cytoskeleton. Several studies have suggested that the epithelial barrier might be compromised in patients with CRS.[87-89] The Gern laboratory suggested the

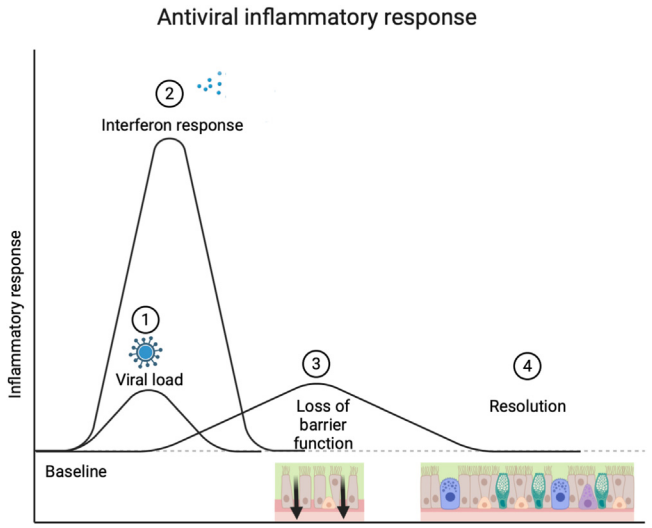


**FIG 1.** Antiviral immune response. Virus binds to sinonasal airway epithelial cells (*1*) and replicates within the cell. This triggers antiviral interferon responses (*2*) and cytokine induction that rapidly increases and can transiently induce loss of epithelial barrier function to allow for cell-mediated viral killing (*3*). These host immune responses then resolve to a homeostatic baseline (*4*). Figure created with BioRender.com.

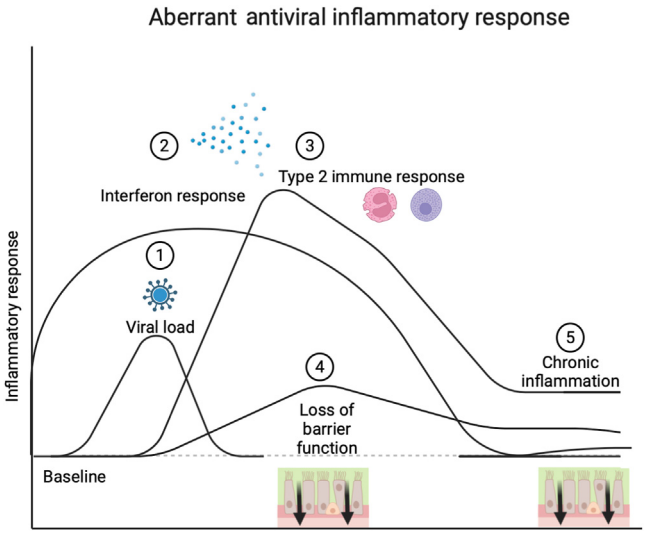


**FIG 2.** Aberrant antiviral inflammatory response. Viruses bind to sinonasal airway epithelial cells and can have an increased viral load that is due either to increased virulence of the virus subtype or to enhanced viral binding (*1*). A delayed interferon response (*2*) results in increased viral replication, and a prolonged interferon response can induce type 2 immune responses characterized by eosinophil and basophil activation (*3*). The release of interferon and type 2 mediated cytokines can increase epithelial barrier permeability and damage, resulting in a prolonged loss of barrier function (*4*) and chronic inflammation (*5*). Figure created with BioRender.com.

interesting hypothesis that loss of barrier function might predispose to viral infections. In their model, reduced airway barrier function in asthmatic individuals might expose viral binding receptors, thereby leading to increased viral binding and replication.[90] Although they speculate that allergic disease might trigger reduced airway barrier function (leading to viral infections), it also possible that repeated viral infections might also result in decreased barrier function. This hypothesis is also supported by work in our laboratory investigating the early pathogenesis of sinusitis. In our study, we followed more than 700 individuals from birth to adulthood in a longitudinal cohort. We found that viral infections and/or colds, allergies, and asthma were significant risk factors for an early-onset chronic sinusitis phenotype.[6]

RV, RSV, and influenza have all been shown to decrease epithelial barrier function via *in vivo* and *in vitro* models. Yeo et al found that after RV infection, TJ (ZO-1, occludin, and claudin-1) mRNA and protein levels were significantly reduced, with a corresponding decrease in transepithelial resistance (TER).[91] Looi et al found similar decreases in TJ proteins after RV infection, and network analyses suggested that this downregulation was due to the expression of antiviral IL-15 responses.[92] RSV infections can also lead to TJ disassembly and alterations to epithelial permeability. A study by Rezaee et al showed TJ and barrier dysfunction after RSV infection through immunofluorescence labeling and a reduction in TER in nasal airway cells.[93,94] Similar findings have been shown *in vivo* through the use of RSV murine models.[95] Similarly, influenza virus has also been shown to decrease levels of TJ proteins and reduce TER.[96,97] This decrease in barrier function is believed to be secondary to antiviral cytokines induced after viral infection.

## SUMMARY

The interaction between viruses and airway epithelia and the resulting host immune response is an important field of research for providing insight into sinonasal inflammation. In this review, we have discussed risk factors, including genetics, virus subtypes, and aberrant immune responses, that might shed light on the pathogenesis of chronic rhinosinusitis. We hypothesize that in acute self-limiting viral infections, an elevated type I interferon response that transiently increases epithelial barrier permeability and orchestrates macrophage, neutrophil, dendritic cell, and natural killer cells to kill virus-infected cells is triggered. Importantly, this response is attenuated shortly after the viral infection and the host immune response returns to a healthy homeostatic state (Fig 1). Alternatively, we hypothesize that aberrant immune responses might result in chronic inflammation of the sinonasal mucosa, thereby contributing to a hallmark of CRS. In this model, a persistently elevated type I interferon response induces type 2 immune responses, characterized by IL-4, IL-5, and IL-13 secretion and recruitment of eosinophils, mast cells, and IgE. Another possibility is that the response might be due to infection by strains with increased virulence, such as RV-C or SARS-CoV2, or increased viral load in subjects with genetic risk factors, such as the rs6967330 SNP in the RV-C receptor CDHR3. In this case, a persistent inflammatory state could increase epithelial barrier permeability and result in the tissue damage and airway remodeling seen in CRS (Fig 2).

The increasing knowledge regarding the molecular pathophysiology of virus-mediated CRS also brings the potential of novel therapeutics. Although honey tea and chicken soup might continue to be the main treatment for respiratory viral infections, it is increasingly clear that more targeted approaches might be beneficial in those at risk for more severe viral disease. The SARS-CoV2 epidemic accelerated approaches for mRNA-based vaccines that would prime the immune system to create antibodies to virus binding, and these have been very successful in reducing the morbidity and mortality associated with

COVID-19. Similar approaches were used in creating the first RSV vaccine, a breakthrough that was recently approved for clinical use by the US Food and Drug Administration. Biologic therapies targeting immune pathways are also available, and it will be interesting to see whether biologics used to treat CRS with nasal polyps, a type 2 immune-mediated disease, also reduces viral exacerbations. Further understanding of the virus-mediated immune responses in CRS might bring us closer to the goal of slowing the progression of this common chronic condition.

## DISCLOSURE STATEMENT

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