

Viral Infections and Susceptibility to Recurrent Sinusitis

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Viral respiratory infection is thought to be the major contributing factor in the pathogenesis of bacterial sinusitis. It is still not clear why some patients suffer from recurrent sinusitis episodes, as information on the exact pathomechanism of how bacterial sinusitis develops as a complication of viral colds is still scarce. In this review, different mechanisms of how a viral infection may predispose some patients to recurrent bacterial sinusitis episodes are presented. Awareness of the fact that different mechanisms may exist behind this single diagnosis of recurrent sinusitis may be of help when diagnostic measures and treatments are planned for these patients.

Introduction

During recent decades, the typical patient with chronic sinus complaints has changed dramatically. Instead of a patient with chronic, unresolving, purulent maxillary sinusitis requiring radical surgery, otorhinolaryngologists are nowadays more and more often faced with a candidate for endoscopic sinus surgery, namely a patient who claims to be suffering from recurrent bacterial rhinosinusitis episodes following each viral respiratory infection [1]. If the patient has an underlying illness, such as gross congenital or acquired immunodeficiency; congenital mucociliary disease (eg, primary ciliary dyskinesia); cystic fibrosis or systemic vasculitis; or granulomatous diseases, the reason for the increased risk of bacterial sinusitis is clear [2••]. However, this is often not the case, and, when examined, these patients are found to have normal nasal endoscopy and no CT evidence of sinus pathology [3]. The information on the exact pathomechanism of bacterial sinusitis is still scarce. However, viral respiratory infection is thought to be the major contributing factor in the pathogenesis of bacterial sinusitis and, therefore, the association of viral upper respiratory infections and susceptibility to recurrent acute bacterial sinusitis, which this review is focused on, is important. Further knowledge would help us to plan proper diagnostic and therapeutic measures for these patients.

Pathophysiology of Viral Respiratory Infections and Bacterial Sinusitis

To understand why some patients may be susceptible to recurrent sinusitis episodes, the pathogenesis of both viral respiratory infection and bacterial sinusitis must first be briefly reviewed.

Viral infection

Viral infections result in complex interactions between the viruses and the host that vary according to the virus. Respiratory viruses spread from person to person by virus-contaminated secretions, either via inhalation or via direct or indirect contact with infected secretions [4]. Mucociliary action transports the viruses to the posterior nasopharynx where the viruses gain entrance to epithelial cells by binding to specific receptors [5••]. Once the epithelium is invaded, viral replication starts. This evokes strong inflammatory and immune response by the host. Release of various mediators, a cellular infiltration, vasodilation, and an increased vascular permeability characterize this response. Increased concentrations of mediators such as kinins; leukotrienes; histamine; interleukin (IL)-1, IL-6, and IL-8; tumor necrosis factor; and RANTES (regulated by activation normal T cell expressed and secreted) have been measured in the nasal secretions of patients with colds [5••]. The nasal cellular immune response includes increased neutrophil counts in the early phase followed later by elevated numbers of lymphocytes and mast cells [6,7]. In addition, cholinergic stimulation leads to increased mucous gland secretion and sneezing [5••]. Although some viruses can cause extensive damage to the ciliated cells and respiratory epithelium (eg, influenza viruses and adenoviruses), others have not been linked with marked histopathologic changes (eg, rhinoviruses).

Clinically, viral respiratory infections constitute an illness in which the severity of symptoms increases rapidly, peaks within 2 to 3 days after infection, and decreases soon after. In healthy volunteers, viral respiratory infections involve nasal congestion, increased amplitude of nasal cycle, prolonged nasal mucociliary time, and mucus hypersecretion [8–12]. Recently, it has been shown that the effect of the viral respiratory infections is not limited to the nasal cavities, but that paranasal sinuses are also almost always affected. Imaging studies performed during the early course of viral respiratory infection in healthy adults and children have shown substantial abnormalities in

the paranasal sinuses that usually resolve spontaneously without antibiotic treatment [13••,14,15•]. Direct spread of virus infection to the sinus, propulsion of fluid by strong blowing of the nose, and collection of mucus in the sinus due to decreased sinus drainage and ventilation have been suggested as possible reasons for these paranasal abnormalities [2••,16,17].

Bacterial sinusitis

In bacterial sinusitis, one or more bacteria are present in high density in the sinus (at least 1000 colony-forming units/mL) [18••]. The same bacteria that colonize the nasal passages and nasopharynx seem to be the most important pathogens causing bacterial sinusitis, namely *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [19]. Information on the exact pathomechanism of how bacterial sinusitis develops as a complication of viral colds is still scarce. The pathologic changes in the paranasal sinuses seen during viral colds indicate impaired sinus drainage and ventilation. The key element in the maintenance of optimal sinus ventilation and clearance is the ostiomeatal complex, a functional unit that comprises maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris, and middle meatus [2••,20••]. Specifically, infundibular and ostiomeatal obstruction due to mucosal swelling, increased mucus production, and impaired mucociliary function during viral infections may contribute to bacterial sinusitis.

Different Mechanisms Linking Viral Infections and Recurrent Sinusitis Episodes

Theoretically, at least four different mechanisms may be found in which viral infection is related to susceptibility to bacterial sinusitis (Fig. 1). First, a tendency to have viral colds frequently may result in recurrent sinusitis episodes. Second, the viral infection may cause pathophysiologic changes, which may predispose some patients to bacterial sinusitis. Third, the symptoms of the viral infections may differ in a way that may increase the risk of being diagnosed with sinusitis. Finally, some patients may have an underlying mucosal abnormality that may make them susceptible to bacterial sinusitis during viral infection.

1. The mechanism of increased viral infections

Acute bacterial sinusitis has been reported to complicate 0.5% to 2.0% of colds in adults [21]. Thus, it is natural to presume that those individuals who suffer from recurrent viral respiratory infections more often have bacterial sinusitis as well. Age and gender are among the factors that have been reported to affect the risk for getting a viral respiratory infection. The incidence of respiratory infection is inversely proportional to age; boys have an increased risk during the first years of life and women during adulthood [22–24]. Genetic factors might affect the susceptibility to respiratory

infections [25,26], but no genetic abnormality has been linked to chronic sinusitis [2••]. Other suggested risk factors comprise exposure to cigarette smoking [27], psychological stress [28], and having a restricted social network [29]. Opinions of whether allergic rhinitis increases the risk for sinusitis vary, but it has been shown that, at least in asthmatic individuals, rhinovirus infections are not more common than in nonasthmatic persons [30].

A useful approach for prevention of virus spread and subsequent illness is education of patients in the importance of infection control (hand washing; avoiding symptomatic individuals and crowds). Infection prevention programs have been shown to reduce the risk for otitis media in day care centers [31]. Similarly, according to one study, specific antiviral treatment for influenza (oseltamivir) reduced the risk for otitis media significantly [32]. In contrast, reports on the effect of virus vaccines (available only for the influenza virus) on otitis media risk contradict [33,34]. To our knowledge, the effect of these treatments or the new antirhinoviral drugs on the risk for contracting sinusitis has not been evaluated in a randomized trial.

2. The mechanism of different pathophysiologic changes

Theoretically, the immunologic, clinical, or microbiologic parameters during viral respiratory infection may differ in some patients, making them more susceptible to recurrent bacterial sinusitis episodes. Potential pathophysiologic mechanisms for synergism between viruses and bacteria include changes in the inflammatory response or respiratory epithelium that may increase bacterial adhesion [35]. The cytokine and mediator profiles in viral respiratory infection and acute and chronic rhinosinusitis are presented to be similar, with the exception of a small increase of eosinophilic cationic protein in chronic rhinosinusitis [2••]. I am not aware that the amount of cytokines and other mediators during viral respiratory infection would have been compared in the sinusitis-susceptible and healthy controls. We compared the structural and cellular changes in the nasal mucosa during acute natural colds and convalescence in patients with allergic rhinitis, patients with susceptibility to sinusitis, and healthy controls [36]. A delayed accumulation of intraepithelial T cells was seen in the allergic and sinusitis-susceptible subjects, indicating a prolonged inflammatory reaction. Moreover, the sinusitis-susceptible subjects had small numbers of mast cells and cytotoxic lymphocytes in convalescence, which may be related to their susceptibility to bacterial complications [36]. Reportedly, the immunologic contents of the nasal secretion have been abnormal in the sinusitis-susceptible subjects as well [37].

The clinical parameters that may hamper sinus ventilation and drainage include changes in the quality or quantity of mucus, lowered mucociliary clearance rate, and obstruction of the ostiomeatal complex. Increased volumes of nasal secretion have been associated with abnormalities in the paranasal sinuses during experimental colds [38].

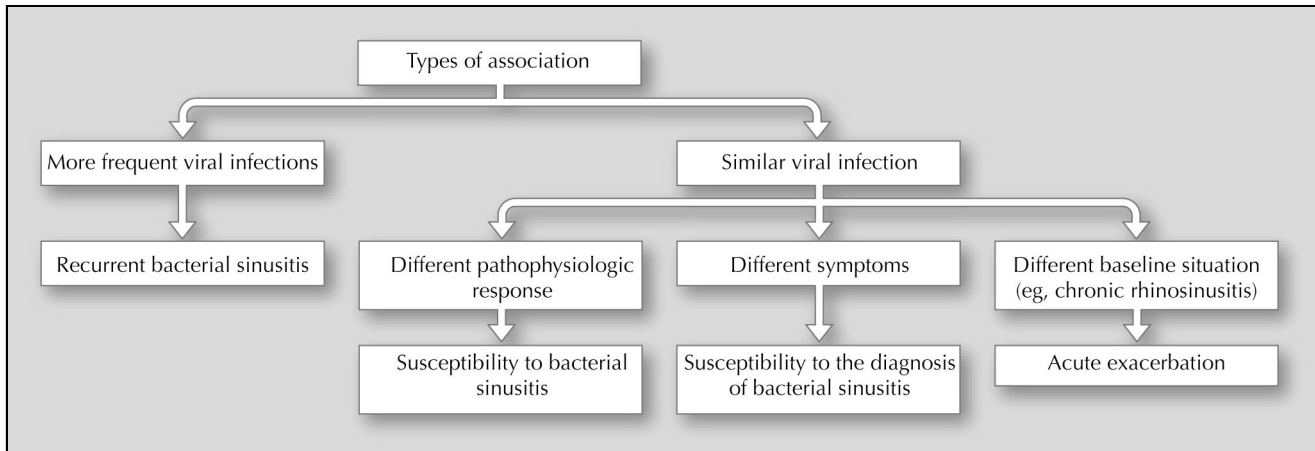


Figure 1. Various theoretical mechanisms of how an acute viral respiratory infection may be related to recurrent bacterial rhinosinusitis episodes.

We observed that abnormal nasal airflow and mucociliary clearance rate associated significantly with pathologic ipsilateral paranasal CT findings during natural colds [12]. However, we saw no marked differences in nasal airflow or mucociliary clearance rate between the sinusitis-susceptible subjects and healthy controls, indicating that other mechanisms are responsible for their impaired paranasal sinus functioning during viral colds [39]. Although certain anatomic variations, such as concha bullosa, nasal septal deviation, and a displaced uncinat process may contribute to ostial obstruction, the equal prevalence of these variations in patients with chronic sinusitis and healthy controls has been thought to indicate that they are not marked risk factors for sinusitis. However, although ostiomeatal complex obstruction and bony variation were equally frequent in sinusitis-susceptible individuals and healthy controls in our series as well, their impact on the functioning of paranasal sinuses was evident in the patients with sinusitis history, which may be associated with the increased risk for bacterial sinusitis [40]. Ostial obstruction is a multifactorial process in which anatomic variations may be one contributing factor. Increased bacterial resistance could be one explanation for the recurrent sinusitis episodes as well [41].

Allergic rhinitis has been suggested to predispose to bacterial sinusitis. Possible mechanisms include enhanced inflammatory reaction, swollen mucosa (which may obstruct the ostium), and allergic reaction to nasal bacterial enterotoxins [2••,42•]. We have shown that subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes in CT scans during viral colds, indicating impaired sinus functioning, which may increase the risk for bacterial sinusitis [43]. Still, there are no published prospective reports on the incidence of infective rhinosinusitis in populations with and without clearly defined allergic rhinosinusitis [2••].

The use of intranasal corticosteroids (potent anti-inflammatory drugs) during viral cold did not decrease

radiographic paranasal sinus abnormalities [14]. However, further knowledge of the immune mechanisms of viral respiratory infection and bacterial sinusitis may allow specific intervention of the inflammatory reaction in properly selected patients. The fact that ostiomeatal obstruction seems to be one major factor in the pathogenesis of bacterial sinusitis suggests that at least some of these patients would benefit from endoscopic sinus surgery.

3. The mechanism of different symptoms during viral infection

The facts that sinusitis is most often preceded by a viral rhinitis and signs and symptoms of viral and bacterial infection overlap makes it difficult to distinguish these two conditions from each other [44]. In theory, those symptoms of viral colds that may increase the tendency of the patients to seek medical attention raise the probability that these patients are diagnosed to have bacterial sinusitis. Facial pain is a symptom that patients do not think of as being associated with common cold but rather with sinusitis. In our series, the sinusitis-susceptible patients were found to have sinusitis-like symptoms, such as facial pain, during viral colds significantly more often and more severely than healthy controls [39]. Facial pain thresholds have been shown to vary in different conditions. For example, subjects with chronic fatigue syndrome are reported to have lower pain thresholds over their maxillary, frontal, and ethmoid regions compared with normal subjects, the possible reason being different neurogenic responses [45].

For these reasons, the history of recurrent acute rhinosinusitis should be examined very thoroughly to find out whether the patient has actually been suffering from bacterial sinusitis episodes [46]. If in doubt, more effective symptomatic treatment of the cold episodes might be tried or if the patient's primary symptom is facial pain, the diagnostic procedures and treatments targeted at this symptom might be utilized [47].

4. The mechanism of exacerbation of underlying pathologic mucosal diseases

Viral infection may promote secondary bacterial infection through exacerbation of underlying airway diseases. Patients with chronic rhinosinusitis may have acute exacerbations characterized by persistent or intermittent episodes of purulent nasal discharge. Here, the role of bacterial agents is clear in contrast with other forms of chronic rhinosinusitis, and the same pathogens as those in acute sinusitis are found [18••]. Thus, if the patient has persistent nasal symptoms, the possibility of chronic rhinosinusitis should be considered. Chronic rhinosinusitis is a complex syndrome whose definition, diagnosis, and treatment have been thoroughly dealt with in the reports of multidisciplinary meetings [2••,18••,48••].

Conclusions

Several different mechanisms exist that may link viral respiratory infections and recurrent bacterial sinusitis episodes. The physicians who treat the sinusitis-susceptible patients must be aware of these mechanisms and consider them when diagnostic examinations and treatments are planned for these patients. Viral respiratory infections are under an intensive research, and with further knowledge of the pathogenesis of viral infections and their bacterial complications, new more specific treatments are going to be presented. The new antiviral drugs and therapies that modify the immune response seem most promising at present. In the future, we need properly designed randomized clinical trials to test their effect in preventing recurrent sinusitis attacks.

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