Otitis Media and Sinusitis

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Introduction

Otitis media (OM) and sinusitis are common diseases for which both children and adults receive medical care each year [1]. Life-threatening complications of these diseases have been minimal following the introduction of antibiotics, but sequelae occasionally occur and may include bony erosion and facial nerve paralysis [2]. The cost of treating these disorders is between $4 and $6 billion per year. In addition, the patient or caregiver is absent from work on an average of 2 days per illness episode, with an estimated cost of $1 billion [3]. The increase in the prevalence of these diseases over the last 15–20 years has led to a similar increase in the use of antibiotics to treat the disease, despite the demonstration of their marginal efficacy in placebo-controlled trials. This is a credible explanation for the selection of antibiotic-resistant bacteria, a phenomenon that is generating increasing concern as inexpensive, first-line antibiotics used to treat common diseases such as OM and sinusitis are becoming ineffective [4].

vURIs are extremely common in children and adults. For most segments of the population, this condition is self-limited and associated with relatively short periods of morbidity. However, in infants, the elderly, and the immunocompromised, infection with some of the causal viruses is associated with significant excess morbidity and, in some cases, even mortality. Also, vURIs are well established as predisposing to other diseases involving the paranasal sinuses, middle ears, and lungs [5–7]. These complications are characterized by a more prolonged time course than that of the precipitating vURI and are often refractory to conventional medical treatment. For example, respiratory synctial virus (RSV) infection, which has been long recognized as a cause of severe lower respiratory illness and complications in infants and young children, was recently shown to signficantly increase morbidity and mortality in the elderly [8]. Medications of questionable efficacy sold for the

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relief of symptoms and signs of vURIs represent a major component of the over-the-counter drug market, and prescription medications for treating associated complications including sinusitis, OM, and pneumonia represent a significant financial burden to society. These costs are compounded by the decreased economic productivity resulting from the large number of days lost to industry and education.
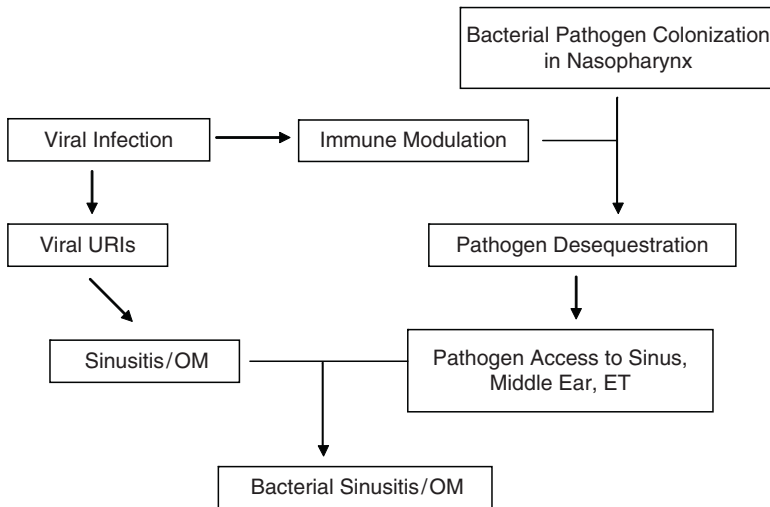
Pathogenesis of Viral Rhinitis

Viruses that cause URIs include rhinovirus (RV), adenovirus, influenza virus (FLU), parainfluenza virus, coxsackie virus, and RSV. Comparative studies of experimental infection of adult humans with RSV, FLU, RV, and coxsackie A virus show that all of these viruses provoke a similar local symptom-sign presentation (with varying degrees of systemic involvement), nasal secretory response, pattern of complications (with varying frequencies), and a panel of elaborated inflammatory mediators (IMs), leukotrienes, and cytokines [9, 10]. Differences that exist among viruses primarily reflect the types of cells that are infected (tissue tropism) and thus the degree to which the infection is localized. For example, although RVs are generally confined to the upper airways by their sensitivity to temperature, RSV can be disseminated to the lung and middle ear by way of the contiguous mucosa and FLU can infect leukocytes via viremic dissemination. These observations suggest that the pathogenesis of the local, cold-like signs, symptoms, and complications is common to the different etiologic agents and most likely represents the consequences of a generalized host response to viral infection of the nasal mucosa.

The most prominent signs and symptoms of vURIs include rhinorrhea, sneezing, nasal obstruction, sore throat, cough, malaise, fever, and sweats [11]. In some studies, the development of airway hyperreactivity has been reported [7], and complications involving the paranasal sinuses are common [5]. Also reported are otologic complications, including Eustachian tube obstruction, middle ear underpressures, and otitis media [12], although cold-like illness or symptoms are not always associated with viral detection by PCR during OM [13]. Most studies have failed to culture virus from the site of the complication (sinus, lung, or middle ear), and the development of complications has been associated with the extension of the inflammatory response as opposed to *in situ* viral infection.

The pathogenesis of symptoms and signs of illness and the pathophysiologies and complications of vURIs have been studied using epidemiological surveys, animal models, and adults experimentally infected with different respiratory viruses. Importantly, similar patterns and magnitudes of pathophysiologic and symptomatic responses to infection were documented for experimental and natural vURIs [11]. A distinct advantage offered by the experimental model over natural infection is its high degree of control over several factors: the health of the subjects; the dose and nature of the infecting agent; and the precise temporal sequence of infection, signs and symptoms, and elaboration of IMs and cytokines.

Early studies of the host response to vURIs focused on the humoral system. High homotypic serum neutralizing IgG antibody titers have been associated with

Bacterial Pathogen Colonization
in Nasopharynx

Viral Infection → Immune Modulation

Viral URIs

Pathogen Desequestration

Sinusitis/OM — Pathogen Access to Sinus, Middle Ear, ET

Bacterial Sinusitis/OM

Fig. 1 Immune interaction and sequelae of viral infections

protection from infection and lessened signs and symptoms [14]. Similarly, high nasal IgA antibody titers have been significantly correlated with a decreased duration of viral shedding. There is also evidence that the cellular immune response may play a role in the pathogenesis of vURIs. Phenotypic and functional changes in the circulating immune/inflammatory parameters have been documented during experimental vURIs [15] (Fig. 1).

Role of Inflammatory Mediators

The role of IMs has been the focus of recent studies on vURI pathogenesis. The similarity between the clinical manifestations of allergic rhinitis and the common cold has prompted repeated attempts to establish a role for histamine and other IMs in the pathogenesis of vURIs. Three generalized methods have been used to provide evidence for a role of IMs and cytokines in the pathogenesis of vURIs: (1) documentation of a time-dependent increase in the concentration of the IM/cytokine (in nasal secretion, blood, or urine) during the period of infection that parallels the symptoms; (2) provocation of signs, symptoms, and mucosal inflammation by topical application of the IM/cytokine; and (3) moderation of the inflammatory process or symptom expression by inhibitors of these IMs/cytokines.

Histamine, a classic mediator of allergic rhinitis, is stored in the granules of tissue mast cells and circulating basophils and is released immediately upon cellular contact with a variety of stimuli. Local histamine in nasal secretions [9] and urinary histamine metabolites can be detected during vURIs [16]. Mucosally applied histamine triggers a full spectrum of rhinitis symptoms and is the only mediator studied that provokes sneezing [17]. Of interest, antihistamine treatment during vURIs

consistently depresses symptoms and signs of sneezing and rhinorrhea, but has little effect on the other aspects of disease expression [18].

Bradykinin is a potent mediator of inflammation and is synthesized locally from precursors delivered with other serum proteins, by transudation. Application of bradykinin to the nasal mucosa provokes rhinorrhea, congestion, facial pain, and sore throat [17]. Kinins were found in the nasal secretions recovered from subjects with experimental and natural vURIs [19]. The concentration and time course of the production of kinins are correlated with symptom severity. However, steroid therapy significantly reduces kinins in nasal lavage fluids, but has no effect on the symptoms, and bradykinin antagonists have not affected the signs and symptoms in a number of experimental RV studies [20].

LTs are potent mediators generated by different cell types that participate in inflammatory reactions. The sulfidopeptide LTs increase the permeability of post-capillary venules and facilitate plasma leakage, edema formation, and cellular diapedesis [21]. LTB_4 is one of the most potent chemoattractants for neutrophils and, to a lesser degree, eosinophils. Both the sulfidopeptide LTs and LTB_4 are potent enhancers of mucus secretion. According to data on a 5-lipoxygenase knockout mouse model, LTs are critically involved in many, but not all, causes of inflammation. Combined with the results reported for mast cell-deficient mice, chemotactic LTs released by mast cells can be shown to be important in neutrophil recruitment during the early acute inflammatory response to insult. Elevated levels of LTs were observed in nasal secretions of children infected with RSV, parainfluenza virus, and FLU and in experimentally infected adults [22]. Moreover, LTs applied directly to the nasal mucosa in noninfected individuals reproduced symptoms of nasal congestion and rhinorrhea [23]. Both 5-lipoxygenase enzyme inhibitors and LTD_4 antagonists have efficacy in treating nasal congestion in allergic rhinitis. Montelukast, an LT receptor antagonist, has been shown to be effective in reducing cough, wheezing, dyspnea, and limitation of activity in infants during RSV infection, however, its ability to prevent vURIs, otitis media, or sinusitis has not been demonstrated [24].

Recent evidence also implicates a role for nitric oxide (NO) in the pathogenesis of vURIs. NO has been shown to decrease and/or inhibit proliferation of several viral systems (through various pathways) in vitro, including FLU, coronavirus (MHV), poliovirus, and HSV-1 (herpesvirus) [25]. Increased concentrations of nasal NO have been reported during vURIs in vivo. Moreover, NO inhibited RV-induced cytokine production and viral replication in a human respiratory epithelial cell line. Recent studies, however, have failed to find an association between NO and signs, symptoms, and complications during experimental vURIs [26].

Role of Neurogenic Inflammation

Mediators of neurogenic inflammation may also play a role in the pathogenesis of vURIs and complications. It is hypothesized that virus infection provokes the release from epithelial cells of IL-11 and endothelins (ETs), which conjointly and

synergistically activate nociceptive nerves, leading to local mucosal axon responses and the subsequent release of inflammatory neuropeptides. These peptides, in turn, cause neurogenic inflammation, which is expressed as nasal irritation, sneezing (nociceptive nerve activation), engorgement of venous sinusoids (mucosal swelling with decreased nasal patency), increased vascular permeability (major source of rhinorrhea fluid), glandular exocytosis, low-grade inflammatory cell infiltration, and reflex obstruction of the eustachian tube and sinus ostia. Evidence also indicates that neurogenic inflammation may be upregulated during allergic inflammation. Nasal secretions obtained from patients with perennial allergic rhinitis (PAR) and healthy controls were compared following whole-nose capsaicin provocation. Subjects from the PAR group exhibited plasma extravasation while the control group did not, likely resulting from neuropeptide release by capsaicin-sensitve fibers [27, 28].

Several lines of evidence support a role for neurogenic inflammation in the pathogenesis and expression of vURIs. These include the following observations: (1) parasympathetic reflexes mediate the glandular exocytosis and mucous hypersecretion; (2) hyperresponsiveness of the nasal mucosa to histamine and cold dry air was reported during RV and FLU infections; (3) viral infection in humans causes release of IL-11, a "neurokine" that increases the sensitivity of nociceptive neurons to activation, increases neural responses to painful stimuli, and provokes bronchial hyperresponsiveness; and (4) ETs are synthesized and secreted by nasal epithelial and glandular cells in response to virus infection [29–31]. In other inflammatory diseases such as asthma and allergic rhinitis, ETs and IL-11 are released, stimulate nociceptive neurons, and recruit parasympathetic reflexes. Also, in allergen challenge studies, the release of substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide is associated with itch, nasal blockage, and rhinorrhea, showing that these nociceptive neuropeptides can be measured in nasal secretions and that their concentrations are related to specific symptoms [32]. Moreover, one study reported that the nasal mucosa of patients with allergic rhinitis contains three times the concentration of substance P as compared with healthy controls [33].

Role of Cytokines

Recent studies have focused on elucidating the role of cytokines in the pathogenesis of vURIs and its complications. The cytokine network provides a complex and highly interactive mechanism for regulation and amplification of the immune system and inflammatory response. During an inflammatory event, proinflammatory cytokines are typically upregulated in a cascading fashion. On the continuum of proinflammatory and immune system-stimulating chemicals, tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) hold central roles. TNF-α is the first cytokine to be upregulated in response to an inflammatory stimulus, with levels peaking within several hours. IL-1 is the second cytokine to be upregulated, with levels peaking within 24–48 h. TNF-α and IL-1 then trigger the sequential

upregulation of other cytokines, including IL-6, IL-8, and IL-10. Interestingly, results from recent studies suggest that the severity of vURI-induced illness and the development of complications are orchestrated by the sequential elaboration of these various proinflammatory cytokines [34–36].

TNF-α and IL-1 also play roles in regulating T-helper type 1 (T_H1) and type 2 (T_H2) immune responses. T-helper lymphocytes can be divided into several subsets including T_H1 and T_H2 cells, which are involved in cellular and humoral immunity, respectively. T_H2 lymphocytes and their cytokines, including IL-4, have been implicated in the pathogenesis of vURI-induced illness and its complications. Increases in local and systemic IL-4 mRNA and protein levels were observed during viral URIs. Several studies reported associations between IL-4 elevations, severity of viral rhinitis, and incidence of virally induced complications [37]. In animal models, overexpression of IL-4 was shown to delay RSV clearance, and treatment with anti–IL-4 was shown to decrease the severity of RSV-induced illness [38].

TNF-α is produced primarily by activated macrophages, induces synthesis of acute phase reactants by the liver, induces fever, and causes the relaxation of the vascular smooth muscle. TNF-α can also activate endothelial cells to upregulate other cytokines and adhesion molecule expression, thus enhancing vascular permeability, cellular adhesion, and procoagulant activity [39]. TNF-α is a proinflammatory cytokine with pleiotropic expression consistent with a primary role in the pathogenesis of virally induced rhinitis. In several studies, release of TNF-α was increased from epithelial cells and monocytes following in vitro infection with respiratory viruses [40]. Elevated levels of TNF-α protein in nasal lavage samples recovered from otherwise healthy infants during primary RSV infection, and from adults following experimental infection with a variety of respiratory viruses have also been reported [41]. Several studies reported that TNF-α production was biphasic with peaks occurring between 6h and 2–3 days following infection with respiratory viruses. Another reported a positive association between local elevations of TNF-α protein and severity of vURIs, particularly RSV infection [42], and a study conducted in our laboratory related elevated TNF-α to the expression of otological complications during FLU infection [39]. These data are consistent with the hypothesis that TNF-α contributes to the pathogenesis of vURIs and complications.

IL-1 is produced by epithelial cells, mononuclear phagocytes, and fibroblasts and shares many of the same activities as TNF-α. The IL-1 family has three members: IL-1α, IL-1β, and an endogenous IL-1 receptor antagonist (IL-1ra). IL-1 has been implicated in the activation of T lymphocytes. Blocking the action of IL-1 has many diverse effects that include inhibiting neutrophil accumulation in the lung tissue of animal models. As with TNF-α, release of IL-1 was increased from nasal epithelial cells following in vitro virus infection [43]. One recent study reported a small increase in IL-1α, a modest increase in IL-1β, and an impressive increase in IL-1ra, in nasal lavages obtained from adults with experimental RV infection [44]. Maximal induction of IL-1α and IL-1β was noted at 48h, whereas, maximal induction of IL-1ra occurred between 48 and 72h. These times corresponded with the peak periods for symptomatology and symptom resolution, respectively. These

data support the hypotheses that IL-1 contributes to the pathogenesis of vURIs, and that IL-1ra plays an important role in disease resolution.

IL-1 and TNF-α interact with other cytokines to modulate inflammation. IL-6 is produced by a wide spectrum of cells in response to a number of stimuli, including IL-1–induced activation of transcription factors. IL-6 mediates many biologic functions that are relevant to virus infection. These include its abilities to act as an endogenous pyrogen, stimulate the acute phase response, stimulate T lymphocytes, induce the terminal differentiation of B lymphocytes, and stimulate immunoglobulin production. IL-6 is a potent regulator of pulmonary inflammation and an important component of biologic homeostasis. Dysregulation is implicated in a wide array of inflammatory and viral disorders. Increases in local IL-6 production were reported during vURIs caused by RV, FLU, and RSV, and coincide with peaks in symptomatology and pathophysiology [35, 36, 45]. Moreover, IL-6 causes significant increases in nasal secretions after topical application [46].

Interleukin-8 is a neutrophil-chemotactic cytokine whose production by monocytes, fibroblasts, endothelial cells, epithelial cells, and neutrophils is induced by IL-1 and TNF-α. In addition to its activity as a potent neutrophil chemoattractant, IL-8 activates neutrophil degranulation and respiratory burst, T lymphocyte chemotaxis, and release of histamine and LTs from basophils. IL-8 has been identified in a number of inflammatory conditions (including nasal allergic responses) at plasma concentrations of up to 1.2 mg/ml, which fall within the range at which neutrophils are stimulated in vitro. IL-8 has been detected in nasal secretions of volunteers infected with RV, FLU, and RSV [35, 36, 47]. Moreover, IL-8 causes marked increases in nasal airway resistance and tissue neutrophilia after topical application, and has been associated with disease severity during experimental RV infection [47, 48].

Interleukin-10 is produced by T lymphocytes, blood monocytes, and tissue macrophages and is considered to be an intrinsic anti-inflammatory and immunosuppressive cytokine. IL-10 inhibits cytokine production by T lymphocytes, mononuclear phagocytes, and natural killer cells. Expression of IL-10 by antigen-presenting cells may have a role in lessening inflammation by inhibiting the synthesis of proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α. This role of IL-10 is supported by its ability to induce T-cell tolerance to the antigen. Indeed, lack of macrophage IL-10 production has been purported to underlie the chronic airway inflammation characteristic of asthma [49]. Increases in local IL-10 production were reported during experimental vURIs, and maximal IL-10 levels typically coincide with the onset of resolution of vURI-induced symptomatology and pathophysiology [50].

Genetic factors likely also play a role in the predisposition of certain individuals to vURIs and their complications, most notably OM and chronic sinusitis. Single nucleotide polymorphisms (SNPs) of cytokine-related genes, which result in high cytokine production, may have a role in promoting inflammation during infection [51]. Severity of RSV infection in infants and adults has been shown to be associated with polymorphism in certain alleles of Interferon-gamma (IFN-γ) and TNF-β genotypes, respectively [52, 53]. Polymorphism of the TNF-β gene has also

been shown to form a component of genetic predisposition to chronic sinusitis [54]. Likewise, OM susceptibility is linked to specific polymorphisms of TNF-α and IL-6 alleles [51].

Several recently developed tools are available for dissecting the role of various proinflammatory cytokines in the pathogenesis of vURIs and its complications. One such tool is the use of animal models of cytokine knockout and blockade. In mice deficient for IL-6 or in those treated with IL-1ra, symptoms of FLU-induced illness were partially reduced [55]. Moreover, mortality was reduced in those animals treated with IL-1ra. Another recently developed tool is cytokine genotyping. Recent studies demonstrated associations between specific cytokine genotypes associated with high production of TNF-α or IL-1β and increased susceptibility to several infectious diseases [56]. These results suggest that certain cytokines are necessary for the development of symptomatology during vURIs and that specific cytokine polymorphisms may be associated with increased susceptibility to viral rhinitis and its complications.

In summary, cytokines promote the initiation, amplification, and persistence of inflammation by their direct cellular effects and by their role in inducing synthesis or release of other inflammatory chemicals in a cascading fashion. A common pathway in vURIs may be the early release of nonspecific, host-alert cytokines, including TNF-α and IL-1. These have both local effects (e.g., depress protein synthesis and upregulate major histocompatibility complex presentation) and systemic effects (e.g., pyrogenic and stem cell maturation) that are expressed as the more general symptoms and signs of illness (e.g., fever and malaise). They also upregulate integrin and selectin expression and thereby mediate the local recruitment of inflammatory cells, which in turn promotes the release or synthesis of IMs (e.g., histamine, bradykinin, eicosanoids, and other cytokines). Some of those IMs initiate neurogenic inflammation and increased vascular permeability (rhinorrhea) and cause sneezing, cough, and nasal congestion. In a cascading and networking fashion, TNF-a and IL-1 also regulate the production of other pro- or anti-inflammatory cytokines via transcription factor activation in an autocrine or paracrine manner. Additionally, there is strong evidence for cross talk between IMs, especially those products of the lipoxygenase pathway and the cytokines. In spite of the data demonstrating an association between cytokines and symptoms of vURIs, the role of these mediators in pathogenesis will not be clear until specific inhibitors are available for use in clinical trials.

Prevention and Treatment

There are a variety of pharmacologic agents currently available for the treatment and/or prevention of vURIs. For certain pathogens, viral rhinitis and its complications can be prevented by effective immunization against the precipitating virus or by effective antiviral prophylaxis or treatment. For example, populations at risk

for severe FLU- or RSV-induced lower respiratory illness can be actively immu-nized with a FLU vaccine or passively immunized with an anti-RSV monoclonal antibody [57, 58]. Moreover, several antiviral agents are available for prophylaxis or treatment [59]. These include ribavirin for RSV and amantadine, rimantadine, zanamivir, and oseltamivir for FLU. Antiviral agents for RV, such as pleconaril, are currently under development and testing. However, at present, the use of immunization or antiviral agents is not applicable to the majority of episodes of vURIs for several reasons: (1) the large number of causative viruses; (2) the high degree of antigenic variability exhibited by most of these viruses; (3) the limited arsenal, high specificity, and significant side-effects of available antivirals; and (4) concerns regarding selection of resistant virus strains during extended antiviral prophylaxis [60].

Symptomatic therapy, including the use of antihistamine, decongestants, and antichoinergics remains the mainstay of treatment for vURIs [61, 62]. Although several large studies of experimental vURIs have confirmed that these agents have some efficacy in treating the symptoms of vURIs, other studies have shown very minimal or no efficacy in the treatment and/or prevention of complications, includ-ing OM and sinusitis.

Numerous studies have examined the efficacy of zinc for the treatment of vURIs. Despite the in vitro effect of zinc on viral replication, there has been no detectable effect of zinc on virus replication in vivo. The effect of zinc on symptoms of viral rhinitis has been inconsistent. Some studies reported dramatic decreases in the duration and severity of symptoms, while other studies have shown no effect [63]. Echinacea has also been widely used for treatment of vURIs, and similar to zinc, efficacy studies have been inconsistent. A recent study by Turner et al. [64] shows that the extract of *Echinacea angustifolia* root had no demonstrable effect on the rates of viral infection or symptom scores following viral challenge.

Conclusions

The majority of current treatments for vURIs and its complications were "borrowed" from other nasal inflammatory diseases (e.g., allergy). The rational development of specific therapies for vURIs and its complications is compli-cated by our incomplete understanding of the disease pathogenesis, the similar expression of illness for different viruses, and the relatively late presentation of identifiable symptoms and signs. Future studies should contribute to a better understanding of the inflammatory responses to vURIs and clarify the roles of the targeted proinflammatory cytokines and neurogenic inflammation in disease expression. This knowledge will lay the foundation for rationally targeted thera-pies directed at host inflammatory or immune responses that have the potential to alter the course of a vURI, suppress disease expression, and limit complications, including otitis media and sinusitis.

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