

Do allergies protect against the effects of a rhinovirus cold?

Key words: Allergy, rhinovirus

There is long-standing speculation that children, and possibly adults, with allergies and asthma get more respiratory infections than the "normal" population does. The evidence supporting this increased susceptibility to respiratory infections has been difficult to ascertain.¹ Nonetheless, there is general agreement that complications of viral respiratory infections are more likely in patients with asthma.²⁻⁶ These observations raise the logical possibility that allergic inflammation promotes the consequences of a viral respiratory infection and thus the likelihood of an asthma exacerbation. Given the frequency and potential severity of virus-induced asthma, investigators have become very interested in the relationship between viral respiratory infections and allergic inflammation.

In this issue of the *Journal of Allergy and Clinical Immunology*, Avila et al (p 923) at the University of California, San Francisco, evaluated their hypothesis that the induction of allergic inflammation in the nose, just prior to rhinovirus inoculation, would amplify the local response to infection in atopic subjects. To evaluate this possibility, allergic subjects were identified and given either repetitive allergen or placebo nasal challenges before an experimental inoculation with live rhinovirus, strain 16. In a carefully designed and executed study, the pretreated (allergen vs placebo) subjects were monitored for cold symptoms, had nasal washings performed for virus culture with fluid analysis of inflammatory cells and cytokines, and had measurements of lung function and bronchial responsiveness.

Given existing concepts, their findings were surprising: pre-exposure of the nose to an allergen both significantly delayed the onset of cold symptoms and reduced the duration of the illness. Furthermore, there was a significant delay in the appearance of nasal leukocytosis and generation of IL-6 and IL-8. Perhaps most interesting, there was an inverse correlation between the percentage of nasal eosinophils at day 0 (the time of rhinovirus type 16 inoculation) and cold symptoms, suggesting that eosinophils protect against the cold virus. Consequently, the authors conclude that "these findings suggest that allergic rhinitis may

not predispose people to more severe colds and indirectly may not increase the likelihood of viral respiratory infection precipitating an asthma exacerbation."

On the surface, the findings of Avila et al seem inconsistent with observations by other laboratories, particularly those of our own. With the same rhinovirus type 16, we had shown that an experimental inoculation of allergic subjects accentuated the intensity of the immediate response to inhaled antigen and increased the frequency of the late-phase allergic pulmonary response as well as enhancing bronchial responsiveness to histamine.⁷ By use of bronchoscopy and segmental antigen challenge, Calhoun et al⁸ demonstrated that an experimental infection with rhinovirus type 16 enhanced mast cell release of histamine and promoted eosinophil recruitment to the allergen-challenged airway segment. Moreover, the enhanced eosinophil response to antigen persisted for at least 6 weeks after the infection.

In trying to explain and understand the differences between the findings of Avila et al and the above studies,^{7,8} a number of issues need to be considered. The nasal antigen challenges before virus inoculation do not replicate a natural exposure to allergen where the dose is smaller but exposure more persistent. In allergen challenge model systems, Avila et al as well as other investigators^{7,8} use high doses of antigen to provoke symptoms and changes in lung function. With high-dose antigen exposure, there is an initial proinflammatory response that is then counterbalanced by anti-inflammatory effects of IL-10 and other modifying mediators. If this scenario were to occur after repetitive high-dose allergen challenges, the local immune environment would tend to down-regulate the inflammatory response, and the consequential effects of a rhinovirus infection would be blunted, as described by Avila et al.

There are, however, convincing data from some experimental infection studies and epidemiologic analyses that the presence of allergic disease is a risk factor for lower airway dysfunction with upper respiratory infections. We have shown that the increase in airway responsiveness during a rhinovirus infection is greater in allergic subjects than healthy individuals.² Furthermore, Duff et al⁹ indicated that a rhinovirus infection plus the presence of IgE antibodies to inhalant allergens were synergistic risk factors for wheezing with colds. In both studies it was the presence of allergic disease and not necessarily a recent allergen exposure that increased the risk for virus-induced airway hyperresponsiveness and asthma. Thus there may be an immune response factor associated with the presence of allergy that causes the accentuated severity of rhinovirus colds seen in patients with allergic disease.

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There is evidence to support this possibility and explain why some subjects with allergic disease may have these adverse effects on airway functions with viral infections. Martinez et al¹⁰ showed that decreased production of IFN- γ by blood cells was associated with an increased likelihood of wheezing with viral illnesses. In addition, Renzi et al¹¹ were able to demonstrate, in infants hospitalized with bronchiolitis, that decreased peripheral blood cell production of IFN- γ was associated with lower pulmonary function and increased bronchial responsiveness after the respiratory illnesses. These studies raise the possibility that some subjects with allergic disease have diminished IFN- γ production, which may then lead to a more severe viral illness and an increased likelihood of adverse effects on airway function. Therefore abnormal airway function during a viral illness may not be the direct result of active allergic airway disease but rather an associated defect in antiviral activity. Further work is necessary to substantiate this possibility.

In analyzing the observations of Avila et al and determining the mechanisms of virus-induced asthma, it is also helpful to understand the host's response to rhinoviruses. Rhinoviruses, in contrast to other respiratory viruses such as influenza or respiratory syncytial virus, do not cause significant cytopathic effects on airway tissue.¹² When rhinoviruses attach to epithelial cells and monocytes/macrophages, they can induce a variety of proinflammatory cytokines, including IL-1 β , IL-6, IL-8, IL-11, TNF- α , RANTES, and GM-CSF.¹³⁻¹⁹ Some of these cytokines, IL-8 and IL-11, for example, have been identified during rhinovirus infection and are associated with changes in airway function,^{20,21} suggesting that the rhinovirus' ability to stimulate proinflammatory cytokine secretion can enhance existing airway inflammation, promote bronchial responsiveness, and increase the likelihood of an asthma exacerbation.

Less well understood are the mechanisms that antagonize the rhinovirus effects. Natural killer cells, CD4⁺ T cells, and CD8⁺ T cells all participate in antiviral immune responses. Cytotoxic CD8⁺ T cells are a major source of IFN- γ during viral infections and exert an antiviral activity by lysing virus-infected cells. Consequently, IFN- γ generation is an important factor in defining the severity of a cold. IFN- γ levels were not detected in the study by Avila et al. Therefore the role of this cytokine as a cause of the observed antiviral activity cannot be fully assessed; whether abnormalities exist in IFN- γ production in the allergic subjects, as discussed above, needs further study.

The authors do, however, point out a number of other important rhinovirus-modulating responses that may account for their observations and shed light on antirhinovirus activity associated with acute allergic inflammatory responses. Allergen challenge of the nose can generate nitric oxide. Recent work by Sanders²² at Johns Hopkins University has shown that nitric oxide inhibits epithelial cell generation of IL-6 and IL-8 by rhinovirus and suppresses virus replication. Therefore it is possible that repetitive antigen challenges stimulate nitric oxide production to inhibit rhinovirus infectivity.

The authors also found an inverse correlation between nasal eosinophils at the time of inoculation and eventual cold symptoms. The role of the eosinophil in the immune response to respiratory viruses, and rhinovirus in particular, is not well defined. Handzel et al²³ were able to show that GM-CSF-treated eosinophils expressed more intercellular adhesion molecule-1, bound rhinovirus type 16, and presented this virus to T-cell clones to cause lymphocyte proliferation. This eosinophil-dependent response can be viewed as proinflammatory in nature. In addition, Kimpen et al²⁴ and Garofalo et al²⁵ were able to demonstrate respiratory syncytial virus activation of eosinophils and the generation of inflammatory mediators. Finally, in a study of children with acute wheezing, either eosinophils or eosinophil activation products in the nasal secretions greatly enhanced the relative risk for wheezing in children with community-acquired rhinovirus infection.²⁶ On the other hand, Adamko et al²⁷ found eosinophils to have antiviral actions in parainfluenza-infected guinea pigs. Domachowske et al²⁸ demonstrated that eosinophil ribonucleases, eosinophil-derived neurotoxins, and cationic protein reduce respiratory syncytial virus infectivity and may be an important antiviral response. Whether eosinophil ribonucleases have similar effects on rhinovirus has not been reported but is of considerable interest as investigators search to unravel and define host-defense mechanisms during an upper respiratory infection and their relationship to proinflammatory or anti-inflammatory actions.

Epidemiologic studies convincingly indicate the importance of viral respiratory infections, including rhinoviruses, to asthma exacerbations. To more fully establish the mechanisms of asthma exacerbations by respiratory viruses, Avila et al have given us new information to consider in this complex, interactive event. Acute allergic responses are associated with activation and recruitment of a variety of cells, including eosinophils, which may, under the right circumstances, modulate the airway viral infection. Like so many immune responses, the eventual consequences of a viral infection (eg, injury or protection) represent a balance, or loss of balance, between the inflammatory and anti-inflammatory (antiviral) responses. When observations such as those of Avila et al emerge that are contrary to current beliefs, it is important to take heed of these findings and examine the host's response to viral illnesses in a new perspective. For the patient with allergic airway disease, it is possible and probable that the eosinophil can wear two hats, "good or evil." When asthma is active, the eosinophil is "evil." In contrast, as in the presence of a parasitic infestation and now possibly a viral respiratory infection, the eosinophil can wear its "good hat." Which "hat" the eosinophil wears may dictate the outcome of the host's response to a viral infection.

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