

Asthma and infections: Is the risk more profound than previously thought?

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In his thoughtful and comprehensive review, Dr Juhn¹ brings to attention potential new and important information about the risks for bacterial infections in patients with asthma and other allergic diseases. The interplay between infections and asthma is of longstanding interest and important, but these factors have been seen primarily as factors that can provoke underlying airway disease. The review by Dr Juhn extends knowledge about infection-asthma interaction and raises the possibility that these patients are also at risk for invasive microbial disease. Although this risk might be rare, it has relevant clinical and public health perspectives of interest and importance to the physician and patient alike.

There is a longstanding appreciation that respiratory tract infections can have profound effects on asthma in terms of disease onset and provocation of exacerbations. Furthermore, these effects on asthma can occur, in part, as a consequence of underlying immune deficiencies in antiviral activity. Asthma exacerbations are most commonly caused by viral respiratory tract infections, a risk factor relationship that is seen most profoundly in children but also occurs in adults. Although virtually any respiratory tract virus can provoke an asthma exacerbation, rhinovirus (ie, the common cold virus) is the most prevalent and has served to highlight the presence of individual patient susceptibility to infections, an underlying theme of Dr Juhn's review.¹

Jackson et al² have shown that frequent wheezing events with rhinovirus infections during the first 3 years of life are a major risk factor for asthma at 6 years of age. Using the Childhood Origin of Asthma birth cohort, Jackson et al² also found allergic sensitization to be a likely prerequisite for rhinovirus-provoked wheezing episodes early in life and a factor to usher in the eventual expression of asthma. Although the precise mechanisms that

underlie this relationship have yet to be fully ascertained, the possibility of diminished antiviral activity has been reported in asthmatic patients, further emphasizing the theme put forth by Dr Juhn¹ that some asthmatic patients might have defective immune function against microbes.

The nature of the proposed immune defect in asthma is the subject of some debate. Wark et al³ reported that epithelial cell generation of IFN- β to rhinovirus was reduced in asthmatic patients,^{3,4} and this has led to speculation that asthma is associated with a primary defect in antiviral responses. Subsequent studies of epithelial responses in asthmatic patients have yielded conflicting results,^{5,6} and it has recently been suggested that interferon responses might be abnormal only in patients with asthma that is not well controlled.⁷ There is further evidence that mononuclear cell interferon responses are reduced in patients with allergic asthma,⁸⁻¹⁰ particularly in airway cells, and mechanisms for this effect are under investigation.

For example, Gill et al⁸ found plasmacytoid dendritic cells from patients with allergic asthma generated less IFN- α when incubated with influenza virus or rhinovirus. The IFN- α response to viral exposure was inversely related to the degree of cell-surface IgE receptor (Fc ϵ RI) expression, and Durrani et al⁹ observed similar relationships between Fc ϵ RI and rhinovirus-induced interferon production in plasmacytoid dendritic cells from asthmatic children. In both studies cross-linking IgE receptors markedly inhibited interferon responses to viruses. The latter finding suggests that allergen exposure and IgE-mediated allergic inflammation in the airways could compromise antiviral interferon responses in patients with allergic asthma. A number of other mechanisms linking asthma to increased susceptibility to infection have been proposed, including defects in epithelial barrier function,¹¹ reduced humoral immune responses,¹² and abnormal mononuclear cell responses to bacteria during early childhood.¹³

Viral respiratory tract infections can also increase the presence of bacteria in the lower airway to further extend and complicate this microbial interaction. Kloepfer et al¹⁴ monitored the appearance of bacteria in nasal secretions from children during the early fall, when they returned to school. The 4- to 12-year-old children were monitored weekly during September by obtaining nasal samples to detect when and under what circumstances respiratory tract viruses and bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, were found. Interestingly, in the presence of rhinovirus, the most common infection at this time of year, *S pneumoniae* was detected, and its presence after a rhinovirus infection was associated with moderate asthma exacerbation. These findings raise the possibility that an infection with rhinovirus, the severity of which might relate to defective immune function, is a risk factor for the appearance of bacteria, such as *S pneumoniae*, in asthmatic patients.

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To investigate the risk of asthma for more severe bacterial infections, Talbot et al¹⁵ at Vanderbilt University used the Tennessee Medicaid program to identify 635 patients with invasive pneumococcal disease and compared their characteristics with those of a larger population of 6350 patients without invasive *S pneumoniae*-induced pneumococcal disease. Two important findings relating to asthma emerged. First, patients with asthma had an increased risk for invasive *S pneumoniae* disease (OR, 2.4). Second, the risk was greater in patients with more severe disease, with an annual incidence of invasive disease of 4.2 episodes per 10,000 persons with high-risk asthma compared with 2.3 episodes per 10,000 persons with low-risk asthma and 1.2 episodes per 10,000 persons if asthma did not exist. High-risk asthma was defined as patients with 1 or more discharges from a hospital or emergency department, 2 or more outpatient visits for asthma, or a prescription for asthma medications. These findings illustrate that patients with less stable asthma are at greatest risk for invasive pneumococcal disease.

In previous work Juhn et al¹⁶ also evaluated risks for serious *S pneumoniae* infections, as defined by (1) physician's diagnosis of pneumonia, (2) isolation of pneumococcus by means of sputum gram staining or culture, or (3) a pneumonia documented by radiography in an allergic population without asthma. An increased risk for pneumococcal infections was found in the atopic group without asthma (14.9%) versus 8.3% in control subjects, suggesting an increased risk for severe pneumonia infections in patients with allergic disease.

Dr Juhn's research group also evaluated the influence of asthma on bloodstream infections with *Escherichia coli*.¹⁷ In a relatively small population the attributable risk for *E coli* bloodstream infection was greater in asthmatic patients (14%) versus control subjects (6%). Although these findings will need to be substantiated in larger populations and with an expanded bacterial panel, they further support the possibility that asthma is associated in selected patients with a greater susceptibility for infections and that this risk for infections is not limited to the lungs.

How should the clinician view the possibility that patients with asthma and other atopic diseases are at increased risk for bacterial infections? First, additional work is needed to explore whether defective immune responses to bacterial infections in asthmatic patients exist, particularly for infections that occur outside the respiratory system. Is the increased susceptibility to bacteria a consequence of greater severity of viral infections? Second, efforts are needed to define the nature of this susceptible host-defense defect. Is it a consequence of allergic inflammation or poor epithelial barrier function? Perhaps an important and immediate aspect for a greater risk of a serious *S pneumoniae* infection in asthmatic patients is the need to consider greater use of pneumococcal vaccination and not limit its use to an older patient group. Although asthmatic patients are not considered to be at high risk for pneumonia, Dr Juhn¹ suggests that it is perhaps

time to reassess this position and make pneumococcal vaccination a part of all adult asthma treatment plans. This appears to be a reasonable suggestion and, from our perspective, a good public health position.

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