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Asthma Exacerbations and Viruses

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SUMMARY

Acute exacerbations of asthma are the major cause of morbidity and mortality of the disease and are difficult to prevent and treat. Asthma exacerbations are associated with several factors, including allergen exposure, air pollution and stress, but the major cause of exacerbations is respiratory virus infection. Respiratory viral infections cause >80% of asthma exacerbations in children and >50% in adults. The most prevalent viruses detected during exacerbations are the rhinoviruses. Respiratory viruses may induce asthma exacerbations through direct effects on their main target, airway epithelium, as well as via systemic immune reaction.

Key words: **asthma exacerbations, respiratory virus infections, rhinoviruses**

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many genetic and environmental factors contribute to the expression of phenotype. The natural hystory of asthma can be strongly influenced by allergens, irritans, or infections that promote inflammation of the smaller airways. Asthma exacerbations are associated with several factors, including allergen exposure, air pollution, and stress, but the major cause of exacerbations is respiratory virus infection. An association between colds and asthma exacerbations has long been recognised, but early studies yielded low virus detection rates of approximately 10%. These studies used virus detection methods that have low sensitivity for rhinoviruses (RV) and coronaviruses, which between them account for the majority of colds. The optimum method for virus detection is with polymerase chain reaction (PCR)-based methods, and studies using PCR have shown that respiratory viruses are responsible for a much higher proportion of asthma exacerbations than was previously suspected (1, 2). Respiratory viruses have also been detected in a high proportion of more severe exacerbations requiring hospitalization. Respiratory viruses can act synergistically with other factors that cause asthma exacerbations. Admission to the hospital with an acute asthma exacerbation is strongly associated with the combination of sensitization and exposure to an allergen, and concurrent viral infection. The presence of high ambient levels of nitrogen dioxide prior to a viral infection is more associated with lower respiratory tract symptoms and greater falls in peak expiratory flow during the exacerbation. Although many respiratory viruses can provoke acute asthma symptoms, RV are most often detected, especially during the spring and fall RV seasons. In fact, the spring and fall peaks in hospitalizations because of asthma closely coincide with patterns of RV isolation within the community. Influenza and respiratory syncytial viruses (RSVs) are somewhat more likely to be associated with acute asthma symptoms in the wintertime, but seem to account for a smaller fraction of asthma flares (3). Furthermore, RV infections are frequently detected in children over the age of two years who present to emergency departments with acute wheezing, and in adults, are detected in approximately half of asthma-related acute care visits (4). In addition to provoking asthma, RV infections can also increase lower airway obstruction in individuals with other chronic airway diseases (eg., chronic obstructive lung disease, cystic fibrosis), and in infants and the elderly. Thus, common cold viruses that produce relatively mild illnesses in most people can cause severe pulmonary problems in selected individuals.

INFLAMMATORY MEDIATORS

Viral infection in asthmatic patients induces more lower respiratory tract symptoms and falls in lung function than that in nonasthmatic patients, but the molecular basis of the greater sensitivity of asthmatic patients to viral infection remains obscure. In vitro infection of airway epithelial cells with rhinovirus induces the secretion of a hoast of inflammatory mediators (5). This also occurs in vivo in both experimental and naturally acquired viral infections. The neutrophil chemokine interleukin (IL)-8 and the proinflammatory cytokine IL-6 have been detected in nasal samples during virus infections in asthmatic patients. In the lower respiratory tract, increases in IL-6, IL-8, and the chemokine regulated on activation, normal T-cells expressed and secreted (RANTES) have been documented in the sputum of asthmatic patients after experimental rhinovirus infection, and IL-8 has been detected in the sputum of children with naturally occurring exacerbations (5, 6). While it is well-recognized that viral infection induces proinflammatory mediators, it is unclear whether the inflammatory response to viral infection differs quantitatively or qualitatively in asthmatic patients (7). One experimental rhinovirus infection study reported increased levels of IL-8 and IL-1 in nasal lavage samples in asthmatic patients but not in control subjects; however, another study reported no differences in IL-6, IL-8, IL-11 and granulocyte-monocyte-colony stimulating factor levels in either nasal lavage or sputum samples. Studies with control subjects of nonasthmatic patients will help to ascertain whether the inflammatory response in asthmatic patients differs from that of healthy subjects (8, 9).

CELLULAR RESPONSE

The production of chemokines by epithelial cells in response to a viral infection leads to an influx of leukocytes into the airway. These cells are an essential part of the innate and adaptive immune responses, but can also result in airway pathology. The release of inflammatory cell products such as neutrophil elastase from neutrophils, major basic protein and eosinophil cationic protein from eosinophils, and reactive oxygen species can cause tissue damage. In stable patients with asthma, the eosinophil and CD4+T cells have been identified as key cellular components of the asthma phenotype, but the cellular response during exacerbations is more heterogeneous (10). Increased levels of sputum neutrophils have been reported in virus-associated exacerbations in adults, whereas exacerbations in which no virus is detected have a higher proportion of eosinophils. Experimental rhinovirus infection studies have reported increased numbers of neutriphils in BAL fluid samples but not in sputum samples (11). Few studies have compared the inflammatory cellular response to viral infection in asthmatic patients and healthy subjects. Increased numbers of lymfocytes and eosinophils in bronchial biopsy specimens are present after experimental rhinovirus infection in both asthmatic patients and healthy subjects, however, at 6 weeks postinfection the eosinophilia persists in the asthmatic patients only. A study of naturally occu-

rring colds in asthmatic patients and healthy subjects found a greater total sputum inflammatory cell count and neutrophil count with a similar differential count in the asthmatic patients (12). Therefore, it would seem that virus-induced exacerbations are at least partially driven by neutrophilic inflammation, and this may account for why therapy with inhaled corticosteroids is effective at suppressing (eosinophilic) airway inflammation in stable patients with asthma but are less successful in preventing exacerbations. New treatments may need to target neutrophils and neutrophil chemokines if virus-induced exacerbations are to be prevented or ameliorated (13).

ANTIVIRAL IMMUNITY AND ASTHMA

The adaptive immune response in asthma patients is associated with a T-helper (Th) type 2 cytokine profile (ie, IL-4, IL-5, and IL-13), whereas adequate antiviral immune response require the Th1 cytokines interferon (INF)-γ and IL-12 (14). Th1 and Th2 immune responses demonstrate mutual inhibition; therefore, within an airway with a preexisting Th2 microenvironment there may be inhibition of Th1 immune responses (5, 9). There is some clinical evidence that imbalances in Th1/Th2 immune responses influence the outcome of viral infections. Peripheral blood mononuclear cells from asthmatic subjects exposed to RV have produced significantly lower levels of IFN-γ and IL-12 with a lower IFN-γ/IL4 ratio than in nonasthmatic patients. Gern et al. showed an inverse relationship between the IFN-γ/IL-5 ratio in sputum samples and both the peak cold symptoms and time to virus clearance from sputum samples in asthmatic patients infected with rhinovirus, suggesting that a stronger Th1 immune response is associated with less severe colds and faster viral clearance (15). There is also evidence that weak Th1 responses are associated with more severe disease in infections with another respiratory virus - respiratory syncytial virus. It has been suggested that this may be another mechanism through which virus infection can exacerbate a preexisting Th2-mediated lung disease (3, 10).

Most immunologic research into asthma has focused on the role of the adaptive immune response in disease pathogenesis, but evidence is emerging suggesting that innate immunity may be imparied in asthmatic patients (13). Wark et al. have shown that bronchial epithelial cells obtained from asthmatic patients support markedly increased rhinovirus replication compared to cells from nonasthmatic patients (16). This is accompanied by reduced apoptosis of epithelial cells in the asthmatic patients and imparied production of the antiviral cytokine IFN-β. Imparied IFN-β production and cells apoptosis result in greater virus replication, eventually leading to cytotoxic cells death with the release of inflammatory mediators and large numbers of intact viral particles. The administration of IFN-β restores the virus protection observed in epithelial cells from normal airways. If confirmed in vivo, it will be interesting to see whether these novel observations translate into new therapies aimed at augmenting or replacing deficient IFN-β production in asthma patients (17).

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EGZACERBACIJE ASTME I VIRUSI

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Sažetak

Akutne egzacerbacije astme su glavni uzročnici morbiditeta i mortaliteta kod ove bolesti i veoma su teške za sprečavanje i lečenje. Egzacerbacije astme udružene su sa više faktora, uključujući ekspoziciju alergenima, aerozagađenje i stres, ali su glavni uzročnici egzacerbacije virusne respiratorne infekcije. One uzrokuju >80% egzacerbacija astme kod dece i >50% kod odraslih. Najprevalentniji virus detektovan tokom egzacerbacije astme je rinovirus. Egzacerbaciju astme respiratorni virusi indukuju direktnim dejstvom na epitel disajnih puteva ili posredstvom sistemskih imunih reakcija.

Ključne reči: **egzacerbacija astme, respiratorne virusne infekcije, rinovirusi**