Etiology of asthma exacerbations

Annemarie Sykes, MBBS, MSc, and Sebastian L. Johnston, MBBS, PhD *London, United Kingdom*

Asthma exacerbations are common, and the major morbidity, mortality, and health care costs associated with asthma are related to exacerbations. The majority are related to viral infection, and although progress has been made in identifying the mechanisms of virus-induced asthma exacerbations, there is still much to be learned. Allergen exposure causes some exacerbations and can participate in virus-induced exacerbations, as can other environmental exposures. A role for atypical bacterial infection in exacerbations is also increasingly recognized. Exacerbations are characterized by airway inflammation, which can differ in type depending on whether it is primarily infective or allergic in origin. An increased understanding of the inflammatory pathways might lead to identification of targets for the development of novel prevention or treatment strategies. (J Allergy Clin Immunol 2008;122:685-8.)

Key words: *Asthma, exacerbations, virus, bacteria, allergen*

Asthma is characterized by stable disease interspersed with periods of exacerbation. Exacerbations are common and characterized by airway inflammation; however, current knowledge of mechanisms involved is incomplete, and therapies used for exacerbations are inadequate.

Exacerbations are associated with environmental factors, such as ozone, nitrogen dioxide,[1] living close to roads,[2] and allergy; however, the majority of exacerbations are related to viral infection, particularly rhinoviruses (Fig 1).

VIRAL INFECTION

Approximately 80% of exacerbations are associated with respiratory tract viral infections, with rhinoviral infection responsible for about two thirds of cases.[3,4] Asthmatic subjects have much more severe lower respiratory tract illness with rhinovirus than healthy control subjects.[5] In a human experimental model of rhinoviral infection, asthmatic subjects also had increased lower respiratory tract symptoms, decreased lung function, and increased bronchial hyperresponsiveness compared with nonasthmatic subjects. Viral load correlated strongly with asthma symptoms and hyperresponsiveness, implicating severity of infection as the main determinant of exacerbation severity.[6] Whether asthmatic subjects are more susceptible to other viral infections remains to be established.

Abbreviations used
IP-10: IFN-γ–induced protein 10
NF-κB: Nuclear factor κB

Interferons in virus-induced asthma exacerbations

The vulnerability of asthmatic subjects to rhinovirus might be due to a defect in interferon production. Interferons are antiviral proteins that have an important role in the innate response to infection, and asthmatic subjects have been shown to have deficient interferon responses to rhinoviruses and other viruses in a range of cells.

IFN-β production in response to rhinoviral infection is known to be reduced in asthmatic bronchial epithelium *ex vivo*, and this impairs an infected cell's ability to undergo apoptosis, allowing increased viral replication.[7] Further interferon deficiencies with viral infection have been documented, including a reduced IFN-α response in PBMCs from asthmatic subejcts[8] and reduced type III, or IFN-λ, responses in bronchial epithelial cells and airway macrophages *ex vivo*. The IFN-λ response was also related to markers of exacerbation severity *in vivo*.[9]

Because this defective innate immune response involves both type I and type III interferons and PBMCs, as well as 2 different lung cell types, it is an important target for further investigation and suggests the potential for a novel treatment or prevention strategy based on administration of interferons.

Mechanisms of virus-induced exacerbations

The mechanisms by which rhinovirus induces exacerbations are not fully understood. Infection induces inflammation, increasing levels of neutrophils, eosinophils, $CD4^+$ cells, $CD8^+$ cells, and mast cells through increased mRNA expression and translation of IL-6, IL-8, IL-16, eotaxin, IFN-γ–induced protein 10 (IP-10), RANTES, and other proinflammatory cytokines.[10] For example, IL-16 is a powerful lymphocyte chemoattractant that also activates eosinophils and macrophages. RANTES is a chemoattractant for eosinophils and lymphocytes, and the release of these and other proinflammatory cytokines can lead to airway hyperresponsiveness, inflammation, and mucus secretion.[11]

Virus-induced asthma exacerbations are chiefly characterized by neutrophilic inflammation. Evidence of neutrophil degranulation and increased lactate dehydrogenase levels are independent

From the Department of Respiratory Medicine, National Heart and Lung Institute, MRC and Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London.

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Reprint requests: Annemarie Sykes, MBBS, MSc, Department of Respiratory Medicine, National Heart and Lung Institute, MRC and Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London, Norfolk Place, London W21PG, United Kingdom. E-mail: Annemarie.sykes@imperial.ac.uk.

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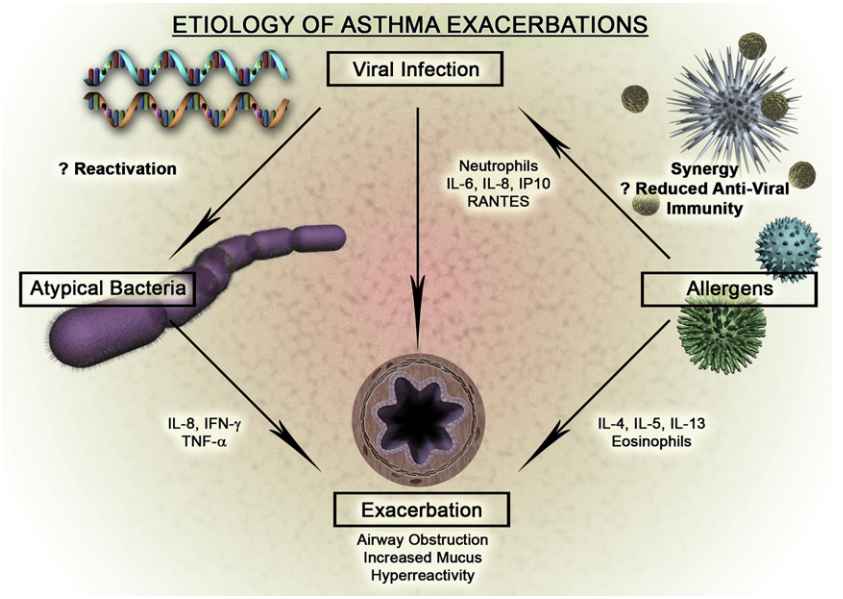

FIG 1. Cause of asthma exacerbations. Viral infection is the predominant cause of asthma exacerbations, and synergy exists between allergen sensitization and viral infection. A link between viral infection and atypical bacteria is increasingly recognized.

predictors of severity,[4] and increased levels of the potent neutrophil chemokine IL-8 are found in exacerbations.[12] Rhinoviral infection also leads to an early release of IP-10, a chemokine involved in T-cell recruitment and mast cell activation. Asthmatic subjects have increased levels of IP-10 in serum; levels correlate with airflow obstruction, and high IP-10 levels are associated with a reduced bronchodilator response to β-agonists.[13]

In experimental rhinoviral infection, viral load was significantly related to lower respiratory tract symptoms and bronchial hyperreactivity. These virologic and clinical outcomes in asthmatic subjects were strongly related to deficient IFN-γ and IL-10 responses and augmented IL-4, IL-5, and IL-13 responses.[6] Although a strong association exists between viral load, severity, and inflammation, this does not prove causation. Until now, a major obstacle to research into the mechanism of rhinoviral infection has been the lack of a small-animal model. Recently, a mouse model of rhinovirus-induced asthma exacerbation has been developed.[14] This should aid investigation into the mechanisms and development of future therapies.

Although differences between asthmatic and nonasthmatic subjects have been identified, much is not yet known, including the contribution of other susceptibility factors, protection factors, or both; the role of proinflammatory cytokine production; and the mechanisms of interaction with atopy. Understanding these mechanisms is pivotal for the development of prevention and treatment strategies.

BACTERIAL INFECTION

Although historically thought to be important, the role of bacterial infection in exacerbations of asthma is less clear than that of viral infection. Recent evidence suggests that asthmatic subjects might also have increased susceptibility to bacterial infection because they have an increased risk of invasive pneumococcal disease,[15] an increased frequency of detection of *Chlamydophila pneumoniae* in stable asthma,[16] and impaired interferon production in response to LPS stimulation.[9] There is therefore increasing interest in the possible role of atypical bacterial infection in asthma exacerbations.

Atypical bacteria

Two studies suggest a contributing role for the atypical bacterium *C pneumoniae* in virus-induced asthma exacerbations. The first reported a strong relationship between levels of *C pneumoniae*–specific IgA in nasal lavage fluid and exacerbation frequency in children.[17] The second reported that 38% of adults attending the emergency department with asthma exacerbations had serologic evidence of *C pneumoniae* reactivation, and those with such evidence had substantially greater lower airway inflammation.[18] It is important to note that both of these studies implicating *C pneumoniae* also had high rates of virus detection (85% and 76%, respectively), and thus *C pneumoniae* is likely to be a contributing factor in virus-induced asthma rather than a primary cause. Studies to determine whether viral infection leads to reactivation of atypical bacterial infection would be of great interest.

C pneumoniae induces cytokine secretion, including TNF-α, IL-1B, and IL-6, from PBMCs[19] and alveolar macrophages.[20] In airway epithelial cells it also induces TNF-α, IL-8, IFN-γ, and nuclear factor κB (NF-κB) with NF-κB activation,[21] and mouse models of *Mycoplasma pneumoniae* and *C pneumoniae* infection cause airway hyperresponsiveness and airway inflammation.[22] Further studies on the importance of atypical bacterial infections in acute exacerbations of asthma are clearly needed.

A double-blind, placebo-controlled study randomized adults with asthma exacerbations to the ketolide antibiotic telithromycin or placebo.[23] The telithromycin group had significantly (approximately 2-fold) greater improvement in asthma symptoms and lung function from exacerbation to the end of treatment. Time to a 50% improvement in symptoms was also 3 days faster in

the telithromycin group.[24] This treatment effect might be the result of treating atypical infection, the anti-inflammatory properties of telithromycin, or both. Macrolides can exert immunomodulatory properties separate from their antibiotic activity by inhibiting synthesis and secretion of proinflammatory cytokines, such as TNF-α, IL-8, and IL-6. Further studies are required to determine whether similar benefits are seen with related macrolide antibiotics.

Allergen sensitization and exposure

Exposure to seasonal allergens has been implicated in sudden asthma-related deaths,[25] *Alternaria* species sensitization and exposure is associated with symptoms,[26] a 200-fold increased risk of respiratory arrest in asthmatic subjects,[27] and house dust mite, cat, and cockroach sensitization are risk factors for emergency treatment.[28] Grass pollen sensitization, or "thunderstorm asthma," has also been associated with epidemics of asthma exacerbations.[29] Thus allergen exposure is also clearly important in a number of acute exacerbations of asthma.

A single study reported allergen-induced exacerbations were characterized by eosinophilic airways inflammation,[4] suggesting corticosteroids are likely to be the most effective current treatment for allergen-induced exacerbations; however, a synergistic interaction between allergen sensitization, allergen exposure, and viral infection has been detected in adult asthmatic subjects during acute exacerbations. Individuals who were sensitized, exposed, and infected had significantly increased risk of admission for exacerbations.[30] This interaction was even greater in children.[31] These data and the fact that steroids can suppress virus-induced proinflammatory molecules might explain why steroids appear effective in many exacerbations.

SUGGESTIONS FOR FUTURE WORK

Despite their clear importance, the mechanisms by which viral infections cause exacerbations are incompletely understood, and a great deal of further work is clearly warranted. Interactions between viruses, other pathogens, air pollution, and allergen exposure require further study.

The interferon deficiencies warrant further investigation to characterize whether they are present in all asthmatic subjects and whether they are acquired or present from birth. The potential to develop interferons as treatment strategies or other therapies that might enhance anti-infective immunity needs to be further explored. Research also needs to address the role of transcription factors, NF-κB, and signaling pathways inducing airway inflammation.

The role of macrolides in asthma exacerbations needs to be further elucidated, particularly whether macrolides could have similar effects to telithromycin.

CONCLUSIONS

An asthma exacerbation can occur as a result of a single cause but more commonly will result from a combination of causes leading to complex inflammatory pathways and induction of airway obstruction. Viral infections are the major precipitant of exacerbations of asthma, and identification of the mechanisms involved should facilitate development of future treatments tailored to the underlying cause. The prevention and treatment of exacerbations needs to be a much greater focus for future research efforts to reduce the massive health care burden related to exacerbations.

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