

Asthma exacerbations: Origin, effect, and prevention

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Asthma is the most common chronic respiratory disease, affecting up to 10% of adults and 30% of children in the Western world. Despite advances in asthma management, acute exacerbations continue to occur and impose considerable morbidity on patients and constitute a major burden on health care resources. Respiratory tract viruses have emerged as the most frequent triggers for exacerbations in both children and adults; however, the mechanisms underlying these remain poorly understood. More recently, it has become increasingly clear that interactions might exist between viruses and other triggers, increasing the likelihood of an exacerbation. In this article we begin with an overview of the health, economic, and social burden that exacerbations of asthma carry with them. This is followed by a review of the pathogenesis of asthma exacerbations, highlighting the various triggers responsible and multiple interactions that exist between them. The final section first addresses what preventative measures are currently available for asthma exacerbations and subsequently examines which of the new treatments in development might lessen the burden of exacerbations in the future. (J Allergy Clin Immunol 2011;128:1165-74.)

Key words: Asthma, asthma exacerbations, viral infection, virus, allergy, allergen, pollutant, bacteria

Asthma is the most common chronic respiratory disease, affecting up to 10% of adults and 30% of children in the Western world. Despite advances in asthma management, acute

Abbreviations used

ACQ:	Asthma Control Questionnaire
BEC:	Bronchial epithelial cell
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
NO ₂ :	Nitrogen dioxide
PEF:	Peak expiratory flow
RSV:	Respiratory syncytial virus
TLR:	Toll-like receptor

exacerbations continue to occur and impose considerable morbidity on patients and constitute a major burden on health care resources. The frequency with which acute exacerbations occur in asthmatic patients varies depending on the definition used for the exacerbation, the severity and degree of control of the underlying disease, and the source of the data. The most comprehensive data on exacerbation incidence comes from therapeutic clinical trials in asthmatic patients. In the OPTIMA trial in patients with mild asthma, exacerbation rates were 0.92 per patient per year in those receiving low-dose inhaled corticosteroids (ICSs) compared with 0.36 in patients receiving high-dose ICSs and a long-acting β -agonist (LABA).¹ In the Formoterol and Corticosteroids Establishing Therapy study in patients with moderate asthma, rates of severe exacerbations were 0.91 per patient per year in those treated with low-dose ICSs and 0.34 in patients receiving high-dose ICSs and LABAs.² In patients with more severe asthma, in a trial of anti-IgE therapy, exacerbation rates over a 48-week period were 0.88 in the placebo group and 0.66 in the treatment group.³ Therefore these data suggest that asthmatic patients receiving optimum treatment should only experience 1 exacerbation every 3 years on average. However, these studies are unlikely to reflect real exacerbation rates because unstable patients and those with frequent exacerbations were excluded, and it is recognized that participation in a clinical trial improves asthma control, even in patients who receive placebo. Also, these figures do not reflect the heterogeneity of exacerbations within the asthmatic population. Some patients will rarely or never experience an exacerbation, whereas others experience frequent exacerbations. A survey of 3151 patients presenting to US emergency departments with acute asthma found that 73% reported at least 1 visit for asthma in the prior year, with 21% reporting 6 or more visits.⁴

Asthmatic patients requiring an emergency department visit or hospitalization are at significantly increased risk of future exacerbations independent of demographic and clinical factors, asthma severity, and asthma control.⁵ However, in a study from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program, the percentage of asthmatic patients with 3 or more exacerbations per year was 5% in the mild group, 13%

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in the moderate group, and 54% in the severe group, suggesting that frequent exacerbations are related to disease severity.⁶ Factors associated with frequent exacerbations include female sex,⁷ obesity,⁵ psychopathology, chronic sinusitis, gastroesophageal reflux, respiratory tract infections, and obstructive sleep apnea.⁸ Therefore some asthmatic patients will experience frequent exacerbations, but it is unclear whether this is independent of traditional measures of asthma control.

Surveys of real-life asthmatic patients indicate that the incidence of exacerbations is much higher than seen in patients recruited for clinical trials. In a survey of 1003 patients in the United States with uncontrolled asthma, 70% had an unscheduled physician's office visit, 36% had an emergency department visit, and 14% had a hospitalization in the last year. Even in patients with controlled asthma, 43% had an unscheduled physician's office visit, 10% had an emergency department visit, and 3% had a hospitalization in the last year.⁹ In the Severe Asthma Research Program cohort 85% of patients with severe asthma had ever attended the emergency department, but even in the mild and moderate groups, the rates of attendance were 58% and 66%, respectively. A survey of 2050 adults and 753 children with asthma in 7 European countries reported that 36% of children and 28% of adults required an unscheduled urgent care visit in the past 12 months. Eighteen percent of children and 11% of adults required 1 or more emergency department visits because of asthma in the past year, and 7% of all patients required overnight hospitalization.¹⁰ These studies suggest that asthma exacerbations are common and frequently result in unscheduled medical care.

Although deaths from asthma are relatively rare, they are frequently associated with poor asthma care and therefore are a leading cause of preventable deaths, often in young people. There were 3447 deaths caused by asthma (3262 adults and 185 children aged 0-17 years) in 2007 in the United States¹¹ and 1400 estimated deaths in 2002 in the United Kingdom.¹² A number of factors have been associated with the fatal or near-fatal exacerbations, including lower socioeconomic status, psychiatric comorbidity, female sex, older age, obesity, smoking, noncompliance with medications, and a previous near-fatal attack.¹³⁻¹⁸ Therefore these factors can be used to identify patients at high risk of asthma mortality and to target appropriate preventative measures.

SOCIAL BURDEN/ECONOMIC IMPACT

The social and economic burden of asthma exacerbations relates to the direct costs of health care use and the indirect costs associated with lost productivity. In the United States in 2007, there were 1.75 million (1.11 million for adults and 0.64 million for children) asthma-related emergency department visits and 456,000 (299,000 for adults and 157,000 for children) asthma-related hospitalizations.¹¹ Hospitalization constitutes about one third of the total \$14.7 billion in US annual asthma-related health care expenditures.¹⁹ The European Lung Foundation has estimated that the cost of asthma in the European Union is €17.7 billion, of which €9.8 billion is related to lost productivity.²⁰ In the Real-world Evaluation of Asthma Control and Treatment survey 24% of adults and 53% of children had missed at least 1 day of work or school, respectively. Therefore the social and economic burden of asthma exacerbations remains considerable.

ORIGINS OF ASTHMA EXACERBATIONS Viruses

Since the early 1970s, viral respiratory tract infections have been reported as triggers for exacerbations of asthma in both adults and children.^{21,22} The development of highly sensitive and specific molecular diagnostic and detection techniques using PCR technology in the 1990s led to greatly improved detection of respiratory tract viruses and allowed a clear demonstration of the important link between viral infections and asthma exacerbations. When PCR is used to supplement or instead of conventional techniques, viruses have been found in approximately 80% of wheezing episodes in school-aged children and in approximately one half to three quarters of acute wheezing episodes in adults.²³⁻²⁶ With the exception of respiratory syncytial virus (RSV) in infants hospitalized with bronchiolitis, rhinoviruses are by far the most frequently detected virus type.

Rhinoviruses are members of the Picornaviridae family, with more than 100 serotypes and no predictable pattern of infection based on serotype. They are the most common cause for the common cold in both children and adults and are distributed worldwide. Methods of virus typing classified rhinoviruses into RV-A and RV-B groups based on genetic sequence similarity and susceptibility to antiviral agents. More recently, a newly identified group, termed RV-C, has been identified based purely on sequencing data. Interestingly, a number of studies suggest that members of the RV-C group might be intrinsically more virulent, have a greater propensity to cause asthma exacerbations, or both than other rhinoviruses^{27,28}; however, further work is needed to better define whether a unique clinical picture is associated with RV-C infections.

Influenza is a common infection during the winter months, frequently reaching local or national epidemic proportions. After the 2009 H1N1 influenza A pandemic, a number of studies highlighted asthma as an important comorbid condition in those infected with this virus. Markers of illness severity, such as hospitalization, admission to the intensive care unit, and mortality in 2009 patients with H1N1 influenza have been shown to be associated with a diagnosis of asthma.²⁹⁻³¹

RSV is the main pathogen causing severe bronchiolitis in infants, with most infections occurring between December and February each year. Differentiating among acute wheeze, bronchiolitis, postbronchiolitis wheeze, and acute exacerbations of asthma is frequently difficult in infants and young children. Subsequently, the interpretation of pediatric studies is complex, and the prevalence of RSV can vary widely from study to study. In an Australian birth cohort study RSV accounted for 16.8% (second behind rhinovirus) of cases of wheezy respiratory tract infections in the first year of life,³² whereas a detection frequency of 27% was seen in a similar British study.³³ RSV in older children and adults is much less frequent; however, it is seen in older adults, in whom it is frequently an underrecognized trigger in acute asthma. A study by Falsey et al³⁴ demonstrated that 7.2% of hospitalizations for asthma in those older than 65 years were associated with RSV infection.³⁴

In addition to rhinoviruses, influenza, and RSV, other respiratory tract viruses, such as coronaviruses, human metapneumoviruses, parainfluenza viruses, adenoviruses, and bocaviruses, have all been detected in subjects with asthma exacerbations. However, in a recent epidemiologic study performed after the discovery of several new respiratory tract viruses, such as bocavirus, the only

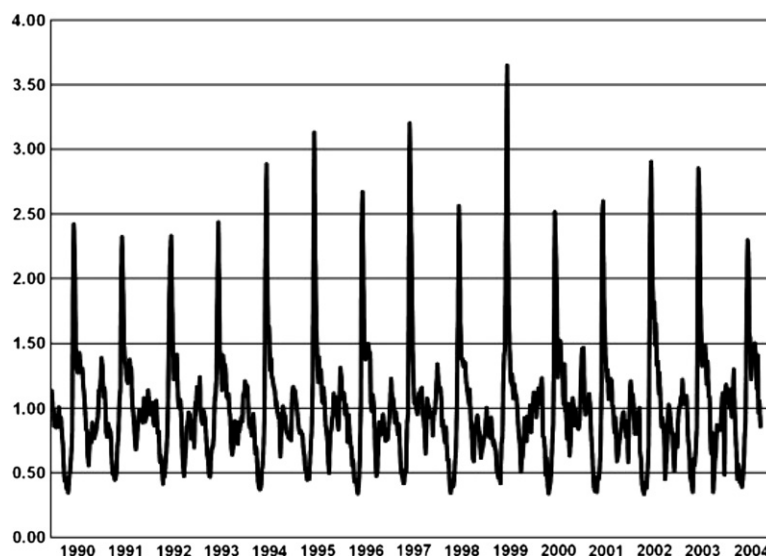


FIG 1. The annual cycle of asthma hospitalization in children aged 2 to 15 years in Canada from 1990 to 2004 expressed as multiples of the within-year weekly mean number of hospitalizations showing epidemic peak occurring in September every year. Reprinted with permission from Sears and Johnston.³⁹

virus type significantly associated with asthma exacerbations in children aged 2 to 17 years were rhinoviruses.³⁵

Seasonal patterns

Exacerbations of asthma are seasonal, and it is important to always take into account the season during which studies on asthma exacerbations are performed. For example, a study in infants carried out in September found no cases of influenza at all,³⁶ whereas a proportion of 20% was seen in another study during the flu season.³⁷

RSV, metapneumoviruses, and influenza viruses (with the exception of the 2009 H1N1 influenza virus) are usually limited to the winter and early spring. Rhinovirus infections can occur throughout the year but are most common in the spring and autumn. In children seasonal peaks in asthma exacerbations occur frequently in autumn, corresponding to the weeks after the start of the school term.^{36,38} This phenomenon has been termed the September epidemic (Fig 1).³⁹ Among older adolescents and young adults, a similar, albeit more blunted, picture is seen, with a peak occurring a week after the school-aged children. In older adults a peak is seen in December to January. The September epidemic was investigated in a case-control study by a Canadian group by limiting recruitment of children with asthma exacerbations to September. Viruses were detected in 62% of cases, with picornaviruses detected in 52% of cases and 29% of control subjects.³⁶

In view of the fact that other environmental exposures, including allergens and pollutants, also vary by season, it seems probable that a combination of factors results in the seasonal peaks seen in exacerbations.

Virus-allergen interactions

A growing body of evidence supports the view that viral infection and allergy interact to increase the risk of an exacerbation. In 2002, Green et al⁴⁰ reported in an adult study that allergen

sensitization, exposure to sensitizing allergens, and respiratory tract viral infection acted in a synergistic manner to significantly increase the risk of hospitalization with acute asthma. Four years later, Murray et al⁴¹ observed even greater synergistic interaction in children. These factors alone, parental smoking, pet ownership, or housing characteristics, did not increase the risk for hospital admission in asthmatic children.

Murray has since shown that levels of IgE antibodies to inhalant allergens in children are associated with an increased risk of asthma hospitalization, with quantification of specific IgE to inhalant allergens being more predictive of exacerbation than using an arbitrary cutoff of serum IgE concentrations to define atopy. Furthermore, a highly significant interaction was observed between IgE concentration and respiratory tract viral infection in increasing the risk of exacerbation.⁴²

Following on from this concept that atopic status is on a spectrum of severity rather than simply a yes or no diagnosis, Simpson et al⁴³ observed that most children classified as atopic by using conventional definitions were clustered into 4 distinct classes. Only one of these classes, termed multiple early sensitization, which comprised approximately a quarter of the atopic children, was significantly associated with risk of hospitalization with asthma (Fig 2).⁴³

As we begin to better define asthma and allergy phenotypes, appreciating the heterogeneity in these disorders, we will better understand the degree of interaction that exists between them.

Bacteria

More than 40 years ago, Berkovitch et al⁴⁴ found evidence of infection with *Mycoplasma pneumoniae* in 18% of children with asthma exacerbations. Since then, numerous studies have investigated a possible association between bacteria (in particular the atypical organisms *M pneumoniae* and *Chlamydomphila pneumoniae*) and asthma exacerbations. However, because many of the methods for detecting these organisms are not standardized, are insensitive, or are nonspecific, the results across

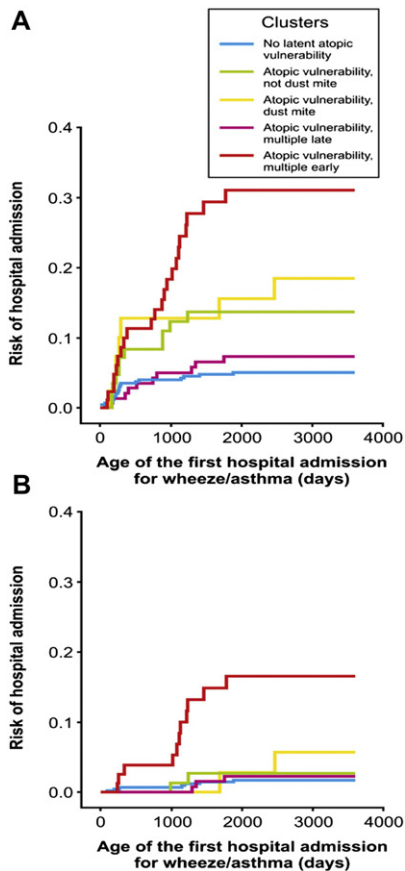


FIG 2. Kaplan-Meier estimates of cumulative risk of hospital admission with wheeze or asthma during the first 8 years of life stratified on 5-class model. **A,** Age at first hospital admission for children who had a hospital admission with wheeze or asthma at any age. **B,** Age at first hospital admission among children who had a hospital admission after age 3 years. A significant increase in the risk of hospital admission with acute asthma is seen only among children in the multiple early class, but not among those in any of the other atopy classes. Reprinted from Simpson et al⁴³ with permission of the American Thoracic Society. Copyright © American Thoracic Society.

these studies have been inconsistent. Johnston and Martin⁴⁵ reviewed 12 such studies and found that 9 of 12 demonstrated an association between infection with either *M pneumoniae* or *C pneumoniae* and exacerbations. These included a study by Allegra et al⁴⁶ reporting evidence of atypical bacterial infection with *C pneumoniae* in 10% of subjects, as well as a prospective study by Lieberman et al⁴⁷ demonstrating *M pneumoniae* infection in 18% of hospitalized asthmatic patients compared with 3% in a matched control group. More recently, Cosentini et al⁴⁸ reported acute infection with *C pneumoniae*, *M pneumoniae*, or both in 38% of 58 patients presenting to the hospital with an asthma exacerbation, and in the TELICAST study 60% were serologically positive.⁴⁹

Freymuth et al⁵⁰ reported more modest infection rates of 4.5% and 2.2% for *C pneumoniae* and *M pneumoniae*, respectively, in a study using PCR on a collection of 132 nasal aspirates from 75 children hospitalized with acute asthma. Another study of 82 children with acute asthma showed similar rates of 5% for both *C pneumoniae* and *M pneumoniae*.⁵¹ No significant differences between asthmatic patients and control subjects have been reported

in several other studies with rates of infection of less than 5%, highlighting the inconsistent nature of the association between atypical bacteria and asthma exacerbations.^{33,40,52}

Wark et al⁵³ found that more than one third of adults presenting with acute severe asthma showed an increase in *C pneumoniae*-specific antibodies, which is consistent with acute infection, reinfection, or reactivation of latent infection with *C pneumoniae*. These subjects exhibited a more intense inflammatory response during the acute exacerbations. Because 76% of these exacerbations were associated with viral infection, these data suggest that *C pneumoniae* might act as a cofactor increasing the severity of virus-induced exacerbations.

Virus-bacteria interactions

Although a large body of data supports an interaction between viruses and allergy, additional interest now exists in whether viruses and bacteria interact to provoke exacerbations. The observation that respiratory tract viral infections commonly precede bacterial infections in both healthy subjects and those with chronic lung conditions is well described.

Oliver et al⁵⁴ identified virus-induced impairment of antibacterial host defense in human alveolar macrophages, suggesting viral infection might alter this function to facilitate additional bacterial infection. After experimental infection with rhinovirus of subjects with and without chronic obstructive pulmonary disease, Mallia et al⁵⁵ recently demonstrated bacterial infection in 65% of volunteers with chronic obstructive pulmonary disease versus around 15% in smoking and nonsmoking control subjects. No bacterial infections were detected at baseline before inoculation. Whether similar findings are seen in asthmatic patients requires further study. Of note is that Huang et al⁵⁶ and Hilty et al⁵⁷ have both highlighted increased and more diverse lower airway bacterial flora in asthmatic patients. Moreover, bacteria have been detected as often as viruses in a recent study of acute episodes of wheeze in children less than 3 years of age.⁵⁸ Similar studies are now required in older children and adults to determine whether bacteria play an important role in these age groups.

Pollution

The effect of air pollutants is generally believed to be less than that of viruses or aeroallergens; however, there is convincing evidence that acute exposure to specific pollutants contributes to symptoms and increases the severity of asthma exacerbations.⁵⁹ A number of pollutants appear to contribute to exacerbations of asthma, with pollutants from the combustion of natural gas and motor fuel, such as nitrogen dioxide (NO₂) and particulate matter, along with ozone, being 3 of the major culprits. Children in particular spend more time outdoors and exercise more, and therefore they breathe a greater amount of pollution per kilogram of body weight than adults. However, even in the indoor environment there are many sources of NO₂, including fireplaces, heaters, and gas stoves. In children with asthma, NO₂ exposure is associated with increased respiratory symptoms,⁶⁰⁻⁶² and increased personal levels of NO₂ are associated with increased severity of virus-induced exacerbations.⁶³ This highlights a potential synergistic effect of these 2 inflammatory stimuli. In addition, controlled exposure studies in asthmatic patients have demonstrated that NO₂ can enhance the allergic response to inhaled allergens.^{64,65} Although it is difficult to dissect out all the factors

that might play a role in the September epidemic, it is possible that seasonal changes in domiciliary air pollution during this period increase the risk of virus-induced exacerbations.

Smoking

Smoking among asthmatic patients is unfortunately common and induces a noneosinophilic pattern of inflammation with relative corticosteroid resistance.⁶⁶ In adults hospital admissions and emergency department visits occur more frequently among cigarette smokers with asthma,⁶⁶ and there is evidence that current smoking is a risk factor for near-fatal and fatal asthma.⁶⁷

The relationship between secondhand smoke and asthma morbidity in children is also well recognized. After the implementation of a public smoking ban in Scotland, Mackay et al⁶⁸ demonstrated a reduction of 18.2% per year in the rate of asthma-related hospitalizations in children. Before the legislation was implemented, admissions for asthma were increasing at a mean rate of 5.2% per year. Studies in Europe and the United States have shown that 40% of children live with a smoker, and in the United States more than 200,000 episodes of childhood asthma per year have been attributed to parental smoking.⁶⁹

Pregnancy

Exacerbations occur in approximately 20% of pregnant women with asthma, yet the mechanisms responsible for this are poorly understood.⁷⁰ Exacerbations can occur throughout pregnancy; however, there appears to be a clustering around the late second trimester. Unsurprisingly, severe asthma appears to be the most important risk factor, and viral infections are likely the most common trigger, although no studies have thus far identified the viruses responsible.^{70,71} Discontinuation of medication (because of the belief it might harm the fetus) might also be an important factor, and current guidelines recommend a stepwise approach to treatment with the aim of maintaining control of maternal asthma throughout the pregnancy.

Psychological factors/stress

A relationship between psychological factors, such as stress and asthma outcomes, has been described for centuries, leading to the term *asthma nervosa*. Severe life events either in isolation or in conjunction with high levels of chronic stress have been shown to significantly increase the risk of exacerbation in children with asthma, and similar findings have been identified in adults.^{72,73}

Sandberg et al⁷² assessed 60 children with asthma over an 18-month period and demonstrated both an immediate risk of exacerbation (within 2 days of the severely negative life event) and a more delayed increase in risk (5-7 weeks after the severe event).

Psychological factors can influence adherence to treatment and clinical follow-up; however, Miller and Chen⁷⁴ demonstrated diminished expression of both glucocorticoid and β_2 -adrenergic receptor genes in asthmatic children experiencing acute and chronic stress. Relative to asthmatic children without comparable stressor exposure, there was a 5-fold reduction in glucocorticoid receptor mRNA and a 10-fold reduction in β_2 -receptor mRNA.

PREVENTION OF ASTHMA EXACERBATIONS

Preventing an exacerbation, as opposed to treating the exacerbation once established, could reduce the social and financial

burden of asthma exacerbations. Several commonly used asthma therapeutics have been demonstrated to reduce the frequency of asthma exacerbations, and some novel biologics have also shown potential.

Vaccination

Respiratory tract viral infection remains the predominant cause of asthma exacerbations,²³ and prevention of infection by vaccination is potentially an effective strategy for preventing exacerbations. No effective vaccine exists for rhinovirus infection, the most common cause of asthma exacerbations,^{23,36} because of its antigenic diversity and multiple serotypes,⁷⁵ and therefore vaccination programs have concentrated mainly on influenza viruses.

Influenza infection has been associated with asthma exacerbations in many studies, and influenza vaccination in asthmatic patients is strongly recommended. Vaccination against pandemic H1N1 influenza is specifically recommended in asthmatic patients. It is safe, is effective at inducing seroprotection,⁷⁶ and can be combined with seasonal influenza vaccination. Asthma was the most commonly identified comorbidity associated with increased disease severity in the recent H1N1 pandemic, emphasizing the importance of the role of vaccination.

However, it should be noted that although several studies do indeed demonstrate a reduction in the number of exacerbations after vaccination, other studies have not shown a clear benefit.⁷⁷⁻⁸⁰

Pharmacologic strategies

ICS treatment reduces the risk of asthma exacerbations. Inhaled budesonide therapy decreased exacerbations by 25% in patients with newly diagnosed, mild persistent asthma, who required fewer courses of systemic corticosteroids compared with patients receiving placebo.⁸¹ High-dose budesonide treatment also reduced asthma exacerbations by nearly 50% in adult asthmatic patients whose symptoms were poorly controlled despite moderate ICS treatment, and the benefits showed dose responsiveness.⁸² A significant reduction in annual severe exacerbations, from 0.77 to 0.29, has also been observed in adult patients with milder asthma not previously prescribed ICS treatment,⁸³ and a reduced exacerbation risk with ICS treatment has also been demonstrated in children.^{84,85} The modes of action of inhaled steroids in preventing virus-induced exacerbations are poorly understood; however, Skevaki et al⁸⁶ demonstrated that the corticosteroid budesonide effectively suppressed rhinovirus-mediated induction of proinflammatory (CCL5, CXCL8, IL-6, and CXCL10) and remodeling-associated (fibroblast growth factor and vascular endothelial growth factor) mediators in bronchial epithelial cells (BECs) in a concentration-dependent manner.

Exacerbations have also been prevented by combined treatment with ICSs and LABAs. Combinations of budesonide and formoterol were more effective than budesonide alone, with annual exacerbations reduced from 0.46 with high-dose budesonide to 0.34 when the same dose was combined with formoterol.⁸² This effect has also been reproduced with other ICS/LABA combinations.^{87,88} Edwards et al⁸⁹ have demonstrated that combination treatment synergistically suppressed induction of rhinovirus-induced chemokines in BECs. Combination therapy with budesonide and formoterol used as both preventer and reliever has also been demonstrated to reduce asthma exacerbations^{90,91} in both adults⁹⁰ and children.⁹²

Leukotriene receptor antagonists might also prevent asthma exacerbations in patients with mild asthma.^{93,94} In children aged 2 to 5 years, Bisgaard et al⁹⁵ demonstrated a reduction in the rate of asthma exacerbations by 31.9% with montelukast compared with placebo over a 12-month period, and a recent trial demonstrated some benefit in acute exacerbations as an add-on therapy.⁹⁶ However, although an earlier trial of montelukast treatment was shown to reduce the risk of exacerbations during the peak that follows summer vacations in children,⁹⁴ a more recent trial did not show any significant benefit in reducing the percentage of days with worsening asthma when initiated at the start of the school year.⁹⁷

mAbs

The development of mAbs to molecular targets identified as important in patients with allergic asthma has shown some early potential in preventing asthma exacerbations.

Anti-IgE. IgE has a key role in the development of allergy by influencing allergen uptake by dendritic cells and activation of mast cells.⁹⁸ The humanized anti-IgE mAb omalizumab is licensed for use in patients with asthma symptoms despite maximal therapy, and treatment results in a reduction in high-affinity IgE receptor density and reduced mast cell degranulation and has been associated with a significant reduction in asthma exacerbations in adult allergic asthmatic patients.⁹⁹⁻¹⁰¹ Omalizumab is effective in reducing asthma exacerbations when given in addition to ICS treatment (odds ratio, 0.52) or during periods of steroid weaning (odds ratio, 0.47)¹⁰¹ and is associated with a reduction in both the number and duration of exacerbations.¹⁰² Omalizumab treatment has also been shown to be effective in children.¹⁰³ In a randomized trial of 6- to 12-year-olds with multiple exacerbations despite ICS treatment, a 43% reduction in clinically significant exacerbations was observed in the treated group over a 1-year period.¹⁰⁴ Adolescents with moderate-to-severe allergic asthma despite ICS treatment have also been reported to require fewer asthma-related systemic corticosteroid courses after omalizumab treatment.¹⁰⁵

Anti-IL-5. IL-5 is a T_H2 cytokine that is essential for the maturation and differentiation of eosinophils. Mepolizumab, an anti-IL-5 mAb, was initially reported to reduce blood eosinophil numbers in patients with mild asthma with no effect on clinical asthma parameters.¹⁰⁶ Subsequent trials in patients with severe asthma demonstrated that, in addition to reduced blood and sputum eosinophil numbers, mepolizumab treatment was associated with reduced asthma exacerbations and improved asthma-related quality of life.¹⁰⁷ In addition, a further study of 20 patients with severe asthma demonstrated a 90% reduction in exacerbation frequency and a 50% reduction in prednisolone requirement after 6 months of mepolizumab treatment.¹⁰⁸ Although encouraging, these studies demonstrate that mepolizumab treatment might be effective in patients with severe steroid-refractory asthma with sputum eosinophilia, but it is unlikely to be helpful in asthmatic patients without evidence of eosinophilia.

Other mAbs. In addition to anti-IgE and anti-IL-5, mAbs have been developed to other cytokines implicated in allergic responses. IL-4 and IL-13 were early targets because of their role in IgE production, suppression of T_H1-mediated immunity, mucin secretion, and adhesion molecule expression. Moreover, after experimental infection with rhinovirus, Message et al¹⁰⁹ observed that augmented IL-4, IL-5, and IL-13 levels were implicated in

the increased severity of asthma exacerbations. Although initial trials of soluble IL-4 receptor blockers were disappointing,¹¹⁰ more recent results have been more encouraging.¹¹¹

A recent trial of lebrikizumab (anti-IL-13) did not demonstrate any significant reductions in the rates of exacerbations; however, in a "high-T_H2" subgroup, the rate of exacerbations was 60% lower in the lebrikizumab group than in the placebo group.¹¹²

TNF- α , a proinflammatory cytokine involved in upregulation of adhesion molecules, mucin secretion, and airway remodeling has also been targeted. Initial investigations in patients with severe asthma with high TNF- α levels treated with the recombinant human TNF- α receptor blocker etanercept demonstrated improvements in FEV₁ and quality of life.¹¹³ Despite an encouraging start, a further study of 309 patients with severe asthma treated with the anti-TNF- α antibody golimumab did not show any change in pulmonary function and exacerbation rates, and the study was discontinued early because of serious side effects.¹¹⁴

Bronchial thermoplasty

Bronchial thermoplasty reduces airway smooth muscle mass by ablating the central airways with radiofrequency energy during bronchoscopy. Early studies demonstrated a reduction in mild exacerbations when performed in patients with severe asthma.^{115,116} In the year after bronchial thermoplasty, mild asthma exacerbations were significantly reduced at 3 and 12 months (0.18 vs 0.35 in the untreated group), which the authors extrapolated to 10 fewer mild exacerbations per year, but no difference was observed in severe exacerbations.¹¹⁷ A significant reduction in severe exacerbations was demonstrated in 288 adults with severe asthma randomized to thermoplasty or a sham procedure; however, this was at the expense of 6% more postprocedure hospitalizations in the treatment group. Reduced emergency department visits and work/school absence was also observed in the thermoplasty group up to 1 year after the procedure, and reduction in severe exacerbations has recently been demonstrated to persist until 3 years.¹¹⁸ Despite these positive results, thermoplasty is unlikely to be widely used because it is very time consuming to administer.

Antibiotics

In recent years, it has become increasingly clear that immunomodulatory effects of macrolide antibiotics exist that are distinct from their antimicrobial actions. Jang et al¹¹⁸ demonstrated reduced expression of intercellular adhesion molecule 1, IL-6, and IL-8 after treatment with erythromycin of rhinovirus-infected epithelial cells. Gielen et al¹¹⁹ showed that pretreatment of BECs with azithromycin significantly increased RV-1B- and RV-16-induced type I and III interferons and interferon-stimulated gene mRNA and protein expression. In addition, azithromycin reduced rhinovirus replication and release.¹²⁰ However, Strunk et al¹²¹ did not demonstrate any superiority of azithromycin over placebo in a study of children in which the primary outcome was time from randomization to inadequate asthma control.

In the case of RSV, treatment of infants with bronchiolitis with clarithromycin led to reduced systemic inflammation acutely and fewer wheezing episodes in the following 6 months.¹²² Although this was a small study, a much larger study of asthmatic adults randomized to receive either telithromycin, a ketolide antibiotic, or

placebo resulted in a greater reduction in asthma symptom scores and lung function in the ketolide-treated group.⁴⁸ Safety concerns have limited the widespread use of telithromycin, and further studies are needed to clarify the position of macrolides in the management of asthma exacerbations.¹²²

Patient education and self-management

One nonpharmacologic approach rightly emphasized in recent years is the role of patient education combined with self-management. It has been convincingly demonstrated that asthma morbidity can be reduced by a self-management program including self-monitoring, a written action plan, regular medical review, and asthma education.¹²³ In adults the risk of being admitted to the hospital decreased by more than 40%, and presentations to the emergency department with asthma decreased by more than 20%¹²³; a similar pattern is also seen for children.¹²⁴ Effective written action plans can be based on symptoms or peak expiratory flow (PEF) and use 2, 3, or 4 action points. PEF-based plans should use personal-best PEF rather than percent predicted PEF because the former consistently improved health outcomes, whereas the latter appears not to do so. In addition, the instructions regarding treatment of exacerbations should include both ICSs and oral corticosteroids.¹²⁵

The ability to predict an exacerbation could have a significant effect on asthma management. Meltzer et al¹²⁶ recently found a significant correlation between the measurements of the Asthma Control Questionnaire (ACQ), a validated composite measure of asthma control, and the risk of future asthma exacerbations. Although it is unrealistic to expect adherence to a full daily diary record, as was required in this study, shorter versions of the ACQ, such as the ACQ-5 or ACQ-6, could be potentially assessed by the patient outside the clinic setting to assess the risk for an asthma exacerbation.

Future treatments

In addition to the mAbs described above, there are a number of other novel targets currently in development with the potential to prevent or reduce the frequency, severity, or both of asthma exacerbations. One such target is inhaled IFN- β . Interest in this target first arose after work by Corne et al,¹²⁷ who demonstrated more severe and more prolonged virus-induced asthma symptoms in asthmatic compared with nonasthmatic subjects. Wark et al¹²⁸ subsequently provided evidence that BECs from asthmatic patients produced lower levels of the type I IFN- β and also showed higher levels of rhinovirus replication. The BECs from asthmatic patients responded to exogenous treatment with IFN- β , exhibiting reduced rhinovirus release and demonstrating that the deficiency in asthmatic cells was associated with production of antiviral IFN- β rather than the actions of IFN- β .¹²⁸ These results suggest that delivery of IFN- β to the lower airways when a cold develops might result in the restoration of antiviral defenses in the lungs of asthmatic patients, limiting the resulting inflammation and thus either preventing or reducing the severity of exacerbations. Importantly, by boosting host defense rather than targeting specific respiratory tract viruses, IFN- β is anticipated to have a broad antiviral activity. The results of a phase 2 proof-of-concept trial of IFN- β therapy are awaited with interest. Similar deficiencies of the antiviral type III IFN- λ s have been observed in asthmatic patients,¹²⁹ and these interferons have also

recently been reported to profoundly suppress allergic airway inflammation.¹³⁰ Thus this family of interferons is also a potential treatment of great interest.¹³¹

Other BEC-derived cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin, are looking like increasingly interesting targets in asthmatic patients, and the next 10 years will likely see a surge in studies of these important mediators. Currently, an mAb directed against thymic stromal lymphopoietin (AMG 157) is in phase 1 development¹³² and antibodies blocking IL-25 and IL-33 activity have been tested with some success in animal models of asthma¹³³ and influenza-induced airway hyperreactivity.¹³⁴

Other interesting targets currently being investigated are Toll-like receptor (TLR) agonists. TLR7 is a receptor for viral single-stranded RNA and signals through the adaptor molecule MyD88, activating transcription factors that induce production of a range of antiviral and inflammatory cytokines, such as interferons and TNF- α .¹³⁵ Kaufman et al¹³⁶ recently tested the effects of the synthetic TLR7 agonist imiquimod in guinea pigs *in vivo*, demonstrating the inhibition of bronchoconstriction within minutes of administration. This novel mechanism to limit bronchoconstriction during respiratory tract infections, in addition to their antiviral properties established some years ago,¹³⁷ makes compounds such as these attractive candidates in asthma treatment. In addition to these exciting targets, there are many other approaches currently in development, such as kinase inhibitors and phosphodiesterase inhibitors¹³⁸; however, a full review of these is beyond the scope of this article.

CONCLUSION

One of the primary goals in the management of asthma is to minimize the risk of future exacerbations. Respiratory viruses are now well accepted as the main trigger for these exacerbations, and despite the emergence of newly discovered viruses, rhinoviruses remain the most common pathogens detected. Understanding the mechanisms provoking virus-induced airway inflammation in asthmatic patients will likely offer significant opportunities for improved disease management. However, the reality at present is that current drugs for the treatment of virus-induced exacerbations are poorly effective, and alternative therapies to modulate viral pathogenesis are desperately needed. To this end, experimental human and murine models of rhinovirus-induced asthma exacerbations have now been developed,^{109,139} offering great potential to increase our mechanistic understanding, as well as providing us with models in which to test potential new therapies. Further study is clearly required to better understand the complicated relationships that exist among viruses, bacteria, and allergic inflammation. Despite the development of newer asthma medications, a recent survey of 2500 asthmatic patients highlighted that in the years between 1998 and 2009, the percentage seeking acute care for their asthma in the preceding 12 months had not changed significantly,^{140,141} This is a sobering truth indicative of how much we still need to do.

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