

Prevention and Treatment of Asthma Exacerbations in Adults



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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Learning objectives:

1. To understand the importance of viral pathogens and allergen exposure in the pathogenesis of asthma exacerbations.

2. To have knowledge of the evidence base underlying the current guidelines for the management of acute asthma exacerbations.

3. To recognize how to assess patients following an acute exacerbation of asthma.

4. To be aware of when to consider initiation of biologics to prevent further exacerbations.

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Asthma exacerbations are major contributors to disease morbidity in patients of all ages. To develop strategies that reduce the disease burden from exacerbations, it is helpful to review current concepts about the risk factors for asthma attacks and current approaches for prevention and treatment. Multiple factors contribute as risks and to the development of asthma

exacerbations, including allergic and infectious processes. Viral respiratory infections, primarily from rhinoviruses, are the dominant exacerbating cause for most asthma patients. Allergic sensitization and allergen exposure contribute directly and enhance susceptibility for respiratory viral infections. Respiratory viruses infect airway epithelium to promote

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Abbreviations used

ICS- Inhaled corticosteroid
IFN- Interferon
IL- Interleukin
ILC2- Immune lymphoid cell type 2
mAb- Monoclonal antibody
OCS- Oral corticosteroid
RV- Rhinovirus
T2- Type 2

underlying type 2 inflammation with eosinophils, the predominant cellular component of increased inflammation. Deficiencies of antiviral interferon responses and generation have been identified that increase susceptibility to viral infections in asthma. Exacerbation treatment focuses on reducing airflow obstruction and suppressing inflammation, followed by improving long-term asthma control. Increasing concern exists regarding the side effects associated with frequent systemic corticosteroid use. A major advance has been the selective use of biologics to prevent exacerbations, primarily in patients with existing type 2 inflammation. Future research to prevent exacerbations is being directed toward antiviral activity and a more encompassing regulation of underlying airway inflammation. © 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:2578-86)

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INTRODUCTION

Acute asthma exacerbations, or attacks, are defined as episodes of worsening of asthma symptoms and pulmonary function. Asthma exacerbations can be an initial manifestation of asthma; however, more commonly, worsening of asthma is part of the disease profile in a patient with known asthma. Asthma exacerbations are a major cause of disease morbidity and personal, familial, and societal burden and are responsible for a significant proportion of asthma-related health care costs. The economic burden of asthma in the United States is large, with an estimated annual per-person incremental cost of \$3,266 (based on 2015 dollars).¹ It is also estimated that the annual per-person cost is nearly threefold greater in the presence of exacerbations. These costs reflect a need for greater amounts of medications, emergency care, and hospitalizations, as well as indirect costs such as absenteeism. Although the frequency of asthma exacerbations can be reduced with current guideline-directed care, these events

are not always fully prevented by conventional treatment with inhaled corticosteroids (ICS) and bronchodilators and remain the Achilles' heel of treatment for many patients. Although the addition of biologics to asthma treatments reduces the frequency of exacerbations, they remain a major cause of disease morbidity and mortality.

A number of factors contribute to asthma exacerbations, including environmental and host-related ones (Figure 1). Primary environmental triggers of exacerbations are viral respiratory tract infections along with allergen or irritant/pollutant exposure. In adults, the impact of viral respiratory tract infections and allergens is not as clear-cut as seen with children and adolescents. The reasons for these differences are not obvious.² In addition, suboptimal adherence to medication is a frequent risk factor often linked to the development of exacerbations. However, there are also certain patient populations who are at higher risk, including those with severe and uncontrolled disease, high levels of type 2 (T2) inflammation, comorbidities, and deficiencies in antiviral activity. Indoor and outdoor pollution remains a risk factor for exacerbations for those living in environments with higher concentrations of such environmental triggers. Low income or poverty places patients at risk for more severe disease and exacerbations. The presence of psychological issues may also increase risk by having an impact on the perception of disease control or adherence to asthma medication use. Ultimately, the greatest risk factor for exacerbations is a history of exacerbations; this creates a vicious cycle in terms of susceptibility and consequences.

Collectively, our focus in this article on the prevention and treatment of asthma exacerbations in adults is based on their multiphased importance to asthma (Table I). We will address causes or contributors to exacerbations, treatment approaches to acute exacerbations, and prevention of future attacks, and future directions for preventing and managing exacerbations.

CAUSES OF ASTHMA EXACERBATIONS

Allergic drivers of asthma exacerbations

Allergic sensitization is a common feature in most patients with asthma,³ but it is more prevalent in children. This association is well appreciated in the development of asthma in at-risk children and as a risk for exacerbation.⁴ To indicate the contribution of allergic sensitization in relation to risks for exacerbations, a number of key observations were made, largely in children and adolescents. Rakes and coworkers⁵ evaluated risk factors in relation to children and adolescents seen for wheezing in an emergency room and found that the presence of allergic sensitization, allergic symptoms, and the detection of rhinovirus (RV) markedly enhanced the risk for wheezing.

In adults, the role of allergen exposure and asthma exacerbations is more difficult to demonstrate in direct relation except with acute exposure to allergens such as cat, for example.

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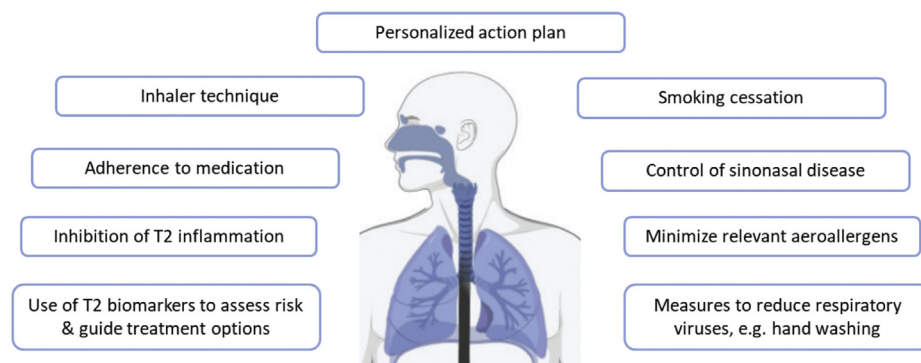


FIGURE 1. Key components in the prevention of asthma exacerbations. T2, type 2.

Nonetheless, allergen sensitization and allergen exposure contribute to risks for exacerbations, or establish conditions that increase the risk for an exacerbation. Lemanske et al⁶ recruited 10 subjects with mild asthma and allergic sensitization to one of three allergens (ragweed, house dust mite, or cat). Measures of airway responsiveness to a histamine aerosol were determined along with the presence of an immediate (15-60 minutes) and late-phase (4-8 hours) response to an allergen challenge. After baseline determinants of immediate and late-phase responses to an allergen challenge were made, subjects were experimentally infected with RV and provocative testing with histamine and allergen was repeated. There was an increased responsiveness to both histamine and allergen. More interesting was a shift in the frequency of the development of a late-phase inflammatory response during the RV infection to eight of 10 subjects compared with pre-RV infections (one of 10). In a subsequent study, bronchoscopy was performed after an airway segmental challenge with allergen; after these values were determined, subjects were experimentally inoculated with RV. During the RV infection, there was an enhanced recruitment of eosinophils as measured in the bronchial lavage fluid. The enhanced allergic responses, airway responsiveness, and late-phase reactions, as well as inflammatory cell recruitment, were still present 4 to 6 weeks after the acute RV infection.⁷ These observations in adults suggest that the allergic reaction to an environmental exposure is enhanced during a viral respiratory infection. This provides insight into interactions between allergic sensitization and viral respiratory infections that increase the risk for an exacerbation.

Efforts to demonstrate a causative role for allergens in asthma by abatement have been difficult in adults, but they were demonstrated in children and adolescents with asthma and by sensitization to cockroach allergen and environmental exposure. To extend the evaluation of a relation between allergen exposure and asthma control, Morgan and coworkers,⁸ based on the findings of Rosenstreich et al,⁹ undertook an intervention study in which exposure to environmental allergens, house dust mite (Der f1 and Der p1), and cockroach, was reduced versus a nonallergen reducing approach in 937 children aged 5 to 11 years. Although reductions in environmental house dust mite and cockroach allergen exposure were associated with improved asthma control (symptom-free days), only in the setting of cockroach allergen reduction was there a significant decrease in unscheduled emergency department visits and hospitalization for asthma. These observations with cockroach-sensitized and

TABLE I. Why are asthma exacerbations important?

Major factor in asthma morbidity and mortality
Significant contributor to cost
Emergency department care
Hospitalization
Patient productivity/societal costs
Risk for progressive loss of lung function
Exacerbations not always prevented by inhaled corticosteroid/long-acting β -adrenoceptor agonist
More frequent in severe disease
Associated with respiratory infections

exposed children provide convincing evidence that allergen exposure can both contribute to risks for exacerbation and cause them.

With other allergens, the contribution and effectiveness of allergen avoidance to improve asthma are more complex and difficult to ascertain.¹⁰ However, allergen avoidance can have a significant effect on airway responsiveness, and with a reduction in this parameter, it is possible to speculate a diminished risk for an exacerbation. Platts-Mills and coworkers¹⁰ identified a small population ($n = 9$) of asthma patients with house dust sensitivity. The patients were confined to hospital rooms for 2 months. During this time, lung function improved, symptoms diminished, and airway responsiveness to a histamine aerosol was lessened.¹¹ These results strongly support a role for allergen exposure in promoting ongoing airway symptoms and likely susceptibility for an exacerbation.

Most aeroallergens associated with asthma severity are indoor allergens (eg, house dust mite, animal dander, and cockroaches). Outdoor allergens can also contribute to aspects of asthma, including susceptibility for exacerbation, but molds are thought to be the most prominent risk factor. In 1991, O'Hollaren and colleagues¹² identified the mold *Alternaria alternata* as a rare but significant factor in severe asthma exacerbations including respiratory arrest. In this study from the Mayo Clinic, 11 patients aged 11 to 25 years were identified in association with an initial episode of a respiratory arrest from asthma. The association between the timing of the sudden onset of severe asthma to the time of year with high atmospheric concentrations of *Alternaria* and demonstration of allergic sensitization to this allergen caused

the authors to raise the possibility that *Alternaria* may be a high-risk allergen for sensitized asthma patients.

The beneficial effects of allergy immunotherapy suggests that the development of immune tolerance to airborne allergens may result in protection from exacerbations.¹³ Using a house dust mite sublingual allergen immunotherapy tablet versus placebo in a double-blind randomized clinical trial,¹⁴ a study with 693 subjects was completed in which the primary end point was the time to the first asthma exacerbation. The trial design was interesting and consisted of treatment stabilization along with the initiation of tablet immunotherapy or placebo. This intervention was followed by an initial reduction of ICS dose by 50% and subsequently 100% reduction of ICS. Compared with placebo, the two dosing regimens of the house dust mite immunotherapy tablet significantly increased the time to a first asthma exacerbation. Presumably, by modifying the allergic response to house dust mite, these investigators were able to demonstrate that sublingual immunotherapy significantly reduced asthma exacerbations despite decreasing background treatment with ICS. This trial with allergen immunotherapy provides evidence for the importance of allergen sensitization to improving disease control and reducing the risk for future exacerbations in adults. The positioning of sublingual allergen immunotherapy to prevent exacerbations in moderate to severe asthma is still under evaluation.

Epidemic thunderstorm asthma¹⁵ is a clear example of allergen-induced asthma exacerbations. The mechanisms that underlie these explosive allergic events, and in some cases death, include an updraft of environmental allergens (ie, rye grass, which is fractured into fine particles by the storm's electrical forces associated with thunderstorms). These fine, easily inspirable allergen-bearing particles are propelled to the ground and inhaled. Because the allergen particles are extremely small, they are capable of penetrating deeply into the airways and can provoke acute, severe, and even fatal wheezing episodes. The severity of these events relates to the allergen, the patient's sensitization to grass, and large allergen loads that can penetrate deeply and over considerable areas of the lung to provoke severe bronchospasm, even in patients with mild disease. O'Hehir and coinvestigators in Australia¹⁶ evaluated preseasonal treatment with grass pollen tablets, compared with conventional asthma treatment, observing that grass tablet immunotherapy significantly diminished asthma exacerbations.

Respiratory viruses as drivers of asthma exacerbations

Respiratory viruses have been recognized as the dominant trigger for asthma exacerbations for several decades; much of the initial supportive data came from pediatric studies. The Childhood Origins of Asthma study recorded 217 exacerbations in which viruses were identified in 69% of episodes; RV was the most common precipitant.¹⁷ Asthma hospitalization rates in children reflect the school calendar with an annual autumn peak, a relationship hypothesized to be mediated by viral transmission. Although this pattern is more variable in adults, a strong link remains with respiratory virus infections: specifically, RV and influenza A are the main culprits.¹⁸

This is also true for the most severe form of exacerbation. An analysis of adults with near fatal asthma exacerbations requiring support with extracorporeal membrane oxygenation revealed that

respiratory viruses were the trigger in over 50% of patients; again, RV was the most common pathogen.¹⁹

Understanding why certain respiratory viruses drive lower respiratory exacerbations in asthma while causing mild upper respiratory symptoms in healthy people has been extensively investigated in recent years. A genetic susceptibility has been considered likely for many years and mutations in the cellular receptor for the RV-C subtype (cadherin-related family member 3) has thus far emerged as the clearest confirmation of this, with specific genotypes linked to more severe asthma exacerbations in children.²⁰

Experimental infection using RV in subjects with and without asthma has offered many insights into both the clinical and differential immune response in asthma, offering mechanistic explanations as to why therapies that target T2 inflammation appear to normalize the patient's response back to that of a common cold. In asthma, experimental infection with RV leads to significant declines in lung function and increased lower respiratory symptoms compared with healthy subjects,²¹ with the level of asthma control at the time of infection directly relating to the severity of the lower respiratory symptoms experienced during the infection.²² These clinical findings mirror the increased risk for exacerbations in patients with poor asthma control in the real world.^{3,23}

Mechanistically, experimental infection with RV along with in vitro studies have highlighted two key interlinked areas of dysregulated immunity that underpin the relation between respiratory viruses and asthma exacerbations. The first relates to an inappropriate activation of T2 pathways in asthma with induction of a plethora of T2 inflammatory mediators including IL-4, IL-5, IL-13, prostaglandin D₂, IL-25, and IL-33 as well as eosinophils.^{21,24-26} The recent success of biologic agents targeting many of these mediators offers some of the clearest evidence to date that the eosinophil and associated cytokines have a central role in virus-induced exacerbation pathogenesis. Indeed, large proportions of patients become completely exacerbation-free²⁷⁻²⁹ despite a high likelihood that most encounter at least one seasonal respiratory virus during the at-risk months.

The epithelial-derived cytokine IL-33 synthesized in response to bronchial epithelial infection appears to be a particularly important mediator in both T_H2 cell and T2 innate lymphoid cell (ILC2)-driven T2 responses to RV and other viruses.^{21,30} In addition, IL-33 has a role in dampening innate and adaptive T_H1-like responses including suppressing the key antiviral cytokine IFN- β .³¹ This mechanism is one of several that contribute to a deficient and/or delayed antiviral immune response in asthma that comprises the second major area of immune dysregulation driving asthma exacerbations³²⁻³⁵ (Figure 2).

During experimental infection with RV, this antiviral deficiency manifests as increased virus load in vivo in asthma compared with healthy subjects.²⁶ An appreciation of this mechanism subsequently led to a clinical trial of inhaled IFN- β , with modest efficacy evident in the more severe, poorly controlled subgroup of patients.³⁶ This therapeutic approach is now being investigated for management of severe COVID-19 infection.³⁷

Research has also demonstrated that there is a synergistic relationship between the impaired antiviral and exaggerated T2 responses in asthma. Duerr and colleagues³⁸ demonstrated that deficiency in signaling via the T1 interferon receptor led to

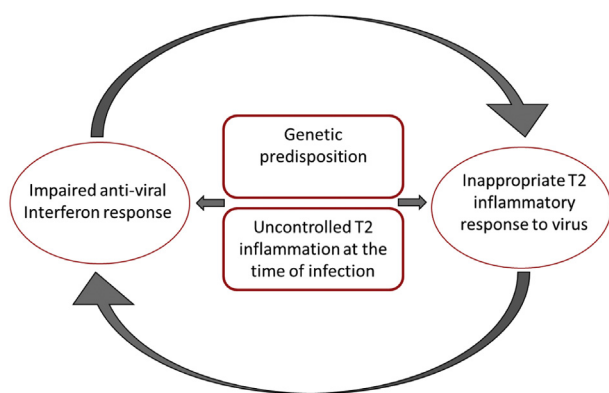


FIGURE 2. Interplay between type 2 (T2) inflammation and anti-viral immunity in asthma.

deregulated activation of ILC2 and infection-associated T2 immunopathology. Altman and colleagues³⁰ reported that the ratio of T2 to T1 interferon gene expression was predictive in determining the risk for a future exacerbation; individuals in the highest quartile for this expression ratio were associated with a significantly shorter time to exacerbation than were individuals in the lower three quartiles.

As described earlier, a synergistic relationship between allergic inflammation and antiviral responses has emerged with impaired interferon responses to RV in asthmatic children correlating with increased FcεRI expression on plasmacytoid dendritic cells and reduced interferon responses in the presence of FcεRI cross-linking.³⁹ In a landmark study, the anti-IgE biologic omalizumab inhibited IgE-mediated inflammation and prevented infection-related seasonal peaks in exacerbations.⁴⁰ Using an experimental RV challenge, Heymann and colleagues⁴¹ administered omalizumab or placebo in a blinded fashion to 20 mildly asthmatic subjects, demonstrating both subjective symptom benefit and blunting the RV-induced blood eosinophilia.

Finally, airway neutrophilia is also increased during virus-induced exacerbations and may have an important role in exacerbation pathogenesis by activating neutrophil extracellular traps (NETosis). However, rather than this process being independent of T2 pathways, NETosis boosts T2 responses, further driving exacerbation severity.⁴²

SARS-CoV2 and asthma exacerbation risk

Unlike RV and influenza, seasonal coronaviruses have rarely been reported as a notable exacerbation trigger in asthma,⁴³ which is in itself revealing. Nevertheless, the gravity of the SARS-CoV2 pandemic has caused great concern among clinicians and people with asthma, who are all too familiar with virus-induced declines in asthma control. Thus far, a consistent signal indicating that patients with asthma are at increased risk from, or experience exacerbation with, SARS-CoV2 has failed to emerge despite some early suggestive data.⁴⁴ Multiple reports describing large cohorts across the asthma spectrum from mild to biologic-treated severe patients have been published suggesting that asthmatic patients appear to experience COVID-19 in a similar manner as that of nonasthmatic ones.⁴⁴⁻⁴⁹ These have included a Spanish cohort of 865 severe asthmatic patients treated with biologic therapies, of whom only two of 865 (0.23%) were

hospitalized with COVID-19⁴⁶; an Italian cohort of 324 patients treated with anti-IL5/5R monoclonal antibody (mAb) therapies, including only one who developed a significant COVID-19 infection⁴⁷; and a UK study of 1365 severely asthmatic patients, reporting 13 COVID-19 hospitalizations.⁴⁸ The uncertainty that remains stems from the potential confounding of these results by the more stringent self-isolation (shielding) among patients with severe asthma compared with the general population. Nonpharmacologic interventions, including increased hand washing and mask wearing, may ultimately have led to the demonstrable reduction in asthma exacerbation rates during the pandemic by inhibiting transmission of other seasonal respiratory viruses. Combined with the possibility of reduced urban pollution, this improved self-management and adherence to ICS highlights what can be achieved by minimizing known exacerbation risk factors.

TREATMENT OF ACUTE ASTHMA EXACERBATIONS

Multiple guidelines are available outlining the management of acute asthma exacerbations.⁵⁰ Assessment of severity and timely administration of corticosteroids to treat the underlying airways inflammation are critical; all other interventions essentially buy time for the corticosteroids to work. Levels of asthma severity and response to treatment are usually determined by a combination of clinical signs and measurements including routine observations, peak expiratory flow rate, oxygen saturation, and, in life-threatening or near fatal asthma, measurements of PaO₂ and PaCO₂.⁵⁰

Despite the ubiquity of their use, there is relatively little evidence to guide dosing and route of administration for systemic corticosteroids. A Cochrane review demonstrated that systemic corticosteroids reduced the need for hospital admission by 60% in an acute exacerbation setting.⁵¹ Some studies have examined the efficacy of high-dose ICS to treat asthma exacerbations.⁵² Currently, there is insufficient evidence to support the use of ICS over systemic corticosteroids for the treatment of acute exacerbations.

The rest of the interventions can be broken down into the three broad categories of bronchodilatation, correction of hypoxia, and ventilatory support. Conventionally short-acting β₂-agonists are administered by either a metered dose inhaler and spacer or a nebulizer,⁵³ often with the addition of ipratropium bromide, which acts as an additional bronchodilator.⁵⁴ Although β₂-agonists are effective bronchodilators, side effects can occur, including tachycardia, dysrhythmias, hypokalemia, and lactic acidosis.⁵⁵ Magnesium sulfate has beneficial effects on smooth muscle relaxation and inflammation and can be given as a single dose in patients with acute severe asthma who have not had a good response to inhaled bronchodilators.⁵⁶ Intravenous aminophylline can be used; however, clinical trial results are conflicting and no definitive study has been performed.⁵⁷ Aminophylline has a narrow therapeutic index, and its use should be confined to patients with a severe exacerbation refractory to initial therapy. There is insufficient evidence to support the use of nebulized or intramuscular adrenaline,⁵⁸ leukotriene receptor antagonists,⁵⁹ or recombinant human deoxyribonuclease⁶⁰ in the management of acute severe asthma.

Many patients with acute severe asthma are hypoxemic and should be given controlled oxygen therapy to maintain oxygen

saturation levels of 94% to 98%.⁵⁰ Controlled oxygen therapy is very important because over-oxygenation may delay the recognition of worsening respiratory failure, worsen CO₂ retention, and reduce cardiac output.⁶¹ There is no evidence to support the routine use of heliox for acute asthma exacerbations.⁶²

Unfortunately, despite appropriate therapy, some patients will develop acute respiratory failure. The exact role of noninvasive ventilation is uncertain for acute asthma (unlike for chronic obstructive pulmonary disease), and it should not be used outside a setting in which immediate intubation and mechanical ventilation are available.⁶³ Invasive mechanical ventilation is reserved for patients with respiratory failure that is progressing despite maximal medical therapy, and attempts should be made to minimize the risks for dynamic hyperinflation.⁶³ Extracorporeal membrane oxygenation improves gas exchange while helping to prevent barotrauma caused by mechanical ventilation and should be considered, when available, in patients with near fatal asthma refractory to conventional ventilation strategies.⁶⁴

PREVENTION OF EXACERBATIONS

An asthma exacerbation should be seen as a red flag indicating poor asthma control that triggers a thorough review of the patient to optimize asthma control and prevent further exacerbations from occurring. There are many reasons why people with asthma have poor control and are at ongoing risk for asthma exacerbations. Using a structured review such as the SIMPLES approach to poorly controlled asthma is a logical way to ensure that all relevant contributory factors are appropriately addressed.⁶⁵ This holistic approach includes a focus on Smoking Status, Inhaler technique, Monitoring, Pharmacotherapy, Lifestyle, Education, and Support.⁶⁵ This set of structured reviews should improve the control of most asthmatic patients and also help determine the subset of people with severe asthma who need specialist referral, apart from the larger cohort with asthma that is difficult to treat. The ability of patients to self-monitor with home measurement of peak expiratory flow and a written personalized asthma action plan is important to identify loss of asthma control early, which can be addressed to prevent the development of a severe asthma exacerbation.⁶⁶

All asthma guidelines propose a stepwise treatment approach with ICS as the default treatment for the vast majority of people with asthma.⁵⁰ The evidence and rationale for the stepwise increase in ICS with the addition of add-on, primarily bronchodilator therapies are well-established.⁵⁰ Unintentional nonadherence owing to poor inhaler technique is one of the main drivers behind poor asthma control.⁶⁷ Inhaler technique should be regularly reviewed and optimized, particularly after an acute exacerbation or change of device.

Antileukotrienes reduce asthma exacerbations.⁶⁸ In a meta-analysis, antileukotrienes decreased exacerbation rates by 41% compared with placebo but were inferior to ICS.⁶⁹

As well as being effective in managing acute exacerbations, oral corticosteroids (OCS) will improve asthma control and prevent future exacerbations. However, the increasingly recognized adverse event profile associated with cumulative OCS exposure⁷⁰ means that in clinical practice, long-term maintenance OCS are the treatment of last resort.⁷¹

A significant percentage of people with presumed mild asthma are prescribed only bronchodilators. People with all severities of asthma can find adhering to daily preventative medication with

ICS difficult and may end up using as-needed bronchodilators in isolation, increasing their risk for exacerbations. One way to counteract this and minimize the risk for future exacerbations is to use anti-inflammatory reliever therapy or maintenance and reliever therapy.⁷² Most clinical studies have examined the clinical utility of combined formoterol and budesonide inhalers as anti-inflammatory reliever therapy; this approach is starting to be included in guidelines.⁷³

ADVANCED INTERVENTION TO PREVENT EXACERBATIONS

In addition to interventions for the acute treatment of exacerbations of asthma, clinicians must evaluate these patients for the potential use of advanced therapy with biologics if control remains poor despite optimizing the basic interventions as outlined earlier. Biologic therapies target inflammatory pathways that are often implicated in exacerbations. Recognition that asthma is a heterogeneous disease with multiple phenotypes driven by the underlying pathobiologic mechanism or endotype has allowed clinicians to target these pathways that lead to exacerbations.^{74,75} Importantly, randomized controlled trials testing these biologics were performed in patients who had an exacerbation-prone phenotype, because a common requirement for these studies was for the patient to have had one or more exacerbations in the previous year. The two broad endotypes that are recognized drivers of exacerbations and are treatable with current biologics are allergen-driven and T2 high.

The allergen-driven endotype is less well-defined by biomarkers but is characterized by a classic history of exposure to an allergen that triggers an exacerbation together with evidence of allergen-specific sensitization. Omalizumab, a humanized anti-IgE mAb, was the first biologic approved for the treatment of asthma. Omalizumab prevents IgE from binding to its high-affinity receptor (FcεRI) found on mast cells and basophils, which dampens the release of proinflammatory mediators and blunts the downstream allergic response.⁷⁶ Over 25 randomized controlled trials showed that in patients with moderate to severe allergic asthma, compared with placebo, omalizumab reduced asthma exacerbations, reduced hospitalizations, and allowed the reduction of ICS dose.⁷⁷⁻⁷⁹

Omalizumab also downregulates the expression of IgE receptor on mast cells, which may have an important role in viral-induced exacerbations. In the Preventative Omalizumab or Step-up Therapy for Fall exacerbations study, pretreatment with omalizumab in children with a history of exacerbations and allergen-specific IgE demonstrated a 52% reduction in exacerbations.⁸⁰ Furthermore, the mechanism appeared to be related to the ability of omalizumab to enhance IFN-α response to RV. Omalizumab reduced the duration and peak level of viral shedding during RV infections as well as the frequency and severity of the infections.⁸¹ These studies suggest that blocking IgE decreases susceptibility to RV infections and therefore may reflect the mechanism of action of omalizumab in reducing asthma exacerbations.

The T2 endotype is characterized by the expression of IL-4, IL-5, and IL-13 by T_H2 and ILC2 cells. It is estimated that T2 inflammation drives exacerbations in most asthmatic patients.⁸² Although there is overlap with the allergen-driven endotype, T2 cytokines have a significant role in driving inflammation in nonallergic eosinophilic asthma as well. Biologic

therapy targeting IL-5 with mepolizumab or reslizumab prevents IL-5 from binding to its receptor on eosinophils and reduces downstream eosinophilic inflammation. In addition, therapy targeting the α subunit of the receptor for IL-5 with benralizumab prevents IL-5 from binding and enhances its ability to engage with Fc γ RIIIa on natural killer cells, causing aggregation around the eosinophil and resulting in antibody-directed cell-mediated cytotoxicity and eosinophil apoptosis followed by phagocytosis by macrophages.⁷⁴

Mepolizumab is effective in reducing exacerbations in asthmatic patients with a baseline eosinophil count of greater than 300 cells/ μ L by approximately 50%.⁸³⁻⁸⁷ In an RV challenge of mild asthma, mepolizumab did not prevent eosinophil activation but enhanced B-lymphocyte, secretory IgA, and macrophage activity.⁸⁸ Reslizumab also reduces exacerbations in asthmatic people by approximately 50%, but in patients with a higher baseline eosinophil count of greater than 400 cells/ μ L.⁸⁹ Benralizumab has been shown to reduce asthma exacerbations by approximately 25% to 60% in asthmatic patients with a baseline eosinophil count of greater than 300 cells/ μ L and offers the advantage of less frequent dosing (once every 8 weeks) compared with mepolizumab and reslizumab.⁹⁰ Both mepolizumab and benralizumab have been shown to have excellent steroid-sparing effects.^{86,91}

Dupilumab is an mAb that binds to the α subunit of the IL4 receptor, preventing both IL-4 and IL-13 signaling, important drivers of T2 inflammation. Dupilumab is effective in reducing exacerbations by approximately 48% with greater efficacy in T2 subsets characterized by blood eosinophilia (>300 cells/ μ L) or elevated fractional exhaled nitric oxide (>25 parts per billion).²⁹ The etiology of exacerbations that were decreased by dupilumab compared with placebo was not evaluated in this study. However, given the role of viruses and IL-13 in driving goblet cell metaplasia, we expect dupilumab to have a significant impact on this phenotype. Confirmatory studies are under way.

The T2 low phenotype is characterized by neutrophilic or pauci-granulocytic airway inflammation; however, there is no approved biologic for T2 low asthma, and thus therapy in this group relies on standard treatment with controller medications. One trial suggests that macrolide therapy with azithromycin may have a role in reducing exacerbations in T2 low patients.⁹² By targeting the epithelial cell-derived cytokine thymic stromal lymphopoietin, which is upstream of the allergic response, it may be possible to affect both T2 high and low pathways and therefore prevent asthma exacerbations in T2 low patients.⁹³

Antivirals such as pleconaril, rupintrivir, and vapendavir have shown minimal or no effects in reducing asthma exacerbations or improving asthma control.⁴³ However, as discussed previously, restoring the interferon response to viruses using exogenous inhaled IFN-beta early after the onset of a cold in patients with a history of viral-induced exacerbations has been evaluated.³⁶ IFN-beta did not improve asthma control compared with placebo, although an exploratory analysis suggested that it may be more effective in a more difficult to treat subset (Global Initiative for Asthma steps 4 and 5).

Additional strategies have involved modulating the microbiota. Both the lung and gut microbiota have a role in protecting against viral and bacterial-induced exacerbations. Viral dysbiosis may contribute to susceptibility to viral infections and may be affected by asthma therapy. In a study comparing atopic asthmatic patients with atopic nonasthmatic patients and healthy

controls, the bronchial microbiome of T2 had significantly lower bacterial burden and the microbiome was linked to responsiveness to corticosteroids.⁹⁴ Whether modulation of the microbiome can prevent exacerbations is unknown, but a large study in children is being evaluated (Oral Bacterial Extract for the Prevention of Wheezing Lower Respiratory Tract Illness Trial).⁹⁵

FUTURE DIRECTIONS

There is a clear desire to personalize therapies for both acute and chronic conditions. Our increased understanding of the interplay between allergic triggers and viral infections that drive most asthma exacerbations, frequently through increased T2 inflammation, make personalization of both exacerbation treatment and future prevention logical next steps. We need to move from treatment directed by symptoms to treatment in both the acute and chronic settings based on objective measurements. Heaney et al⁹⁶ demonstrated the possibility of using a composite biomarker in chronic asthma management, and measurement of biomarkers of T2 inflammation in conjunction with measurement of lung physiology should be used to help guide acute asthma management. Novel methods for rapidly assessing for viral and/or bacterial infection may further allow personalization of treatment in the future.

The development of effective biologics targeting T2 inflammation has led to the clinical dilemma of how to manage patients who experience exacerbation while receiving biologics. For instance, does a patient treated with benralizumab, which depletes tissue eosinophils, require OCS at the time of symptom worsening? Studies are under way to better understand the exact nature of exacerbations in patients established in the treatment of biologics, which will further help to personalize care.⁹⁷

CONCLUSIONS

Exacerbations remain the main cause of morbidity and mortality in asthma and should be considered a red flag to ensure that asthma care is optimized to prevent future risk. Our improved understanding of the pathogenesis of exacerbations, which are frequently caused by worsening T2 inflammation driven by viral infections, with or without allergen exposure, has allowed the development of novel targeted biologics, which significantly decrease the risk for future exacerbations. The next paradigm shift in preventing and managing asthma exacerbations will be driven by moving from a one-size-fits-all approach for this heterogeneous disease toward personalized therapies.

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