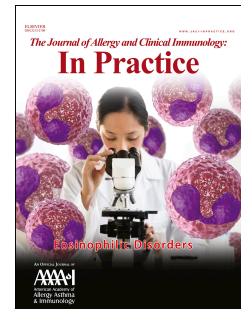


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Exacerbation-Prone Asthma

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Abstract

Patients who are prone to exacerbations of asthma experience significant costs in terms of missed work and school, acute care visits and hospitalizations. Exacerbations are largely driven by environmental exposures including pollutants, stress and viral and bacterial pathogens. These exposures are most likely to induce acute severe “asthma attacks” in high-risk patients. These personal risk factors for exacerbations can vary with the phenotype of asthma and age of the patient. In children, allergic sensitization is a strong risk factor, especially for those children who develop sensitization early in life. Airway inflammation is an important risk factor, and biomarkers are under evaluation for utility in detecting eosinophilic and type 2 inflammation and neutrophilic inflammation as indicators of risk for recurrent exacerbations. Insights into inflammatory mechanisms has led to new approaches to prevent exacerbations using monoclonal-antibody-based biologics that target specific type 2 pathways. Challenges remain in developing an evidence base to support precision interventions with these effective yet expensive therapies, and in determining whether these treatments will be safe and effective in young children. Unfortunately, there has been less progress in developing treatments for acute exacerbations. Hopefully, greater understanding of mechanisms relating airway viruses, bacteria, mucin production and neutrophilic inflammatory responses will lead to additional treatment options for patients experiencing acute exacerbations.

Key words: exacerbation-prone asthma, steroid-resistant, precision interventions

Introduction

Asthma exacerbations are frequently triggered by acute exposures to environmental stimuli (the seed) in the presence of incompletely controlled airway inflammation (the soil); both components are needed to make a productive garden, and have been reviewed recently in this journal.¹ Exacerbation prone asthma is often defined as having two or more bursts of oral corticosteroids a year despite the use of at least two controller medications, including a medium or high dose ICS.² A systematic approach to the care of these patients in clinic includes confirmation of the diagnosis, management of contributing comorbid conditions, and optimization of factors related to medication adherence and environmental control (summarized in the 2019 GINA guidelines, <https://ginasthma.org/severeasthma/>). Despite great advances in the understanding and treatment of asthma, many patients with severe disease continue to have frequent exacerbations,³⁻⁶ and the lack of predictive biomarkers and a personalized approach to treatment remain unmet needs.⁷ Much of the current literature in this area lacks longitudinal follow-up to document stability of these phenotypes. Compounding this problem, there is growing recognition that the dose responses of ICS flatten quickly above the low dose range,⁸ and that even short exposures to OCS have significant risks of major adverse events.⁹ Fortunately, the pipeline of therapeutics for patients with severe disease continues to expand.¹⁰ The scope of this review is to examine the environmental and personal risks as phenotype-subsets of exacerbation prone asthma, discuss how this information modifies current management strategies, and provide a vision for future research to better define the molecular endotypes and associated targets for therapeutic development.

Risk Factors

Environmental Risks

The bulk of studies in this area relate to the inception of asthma and contributions to ongoing exacerbations in patients with mild-to-moderate disease at baseline. Although this has been

reviewed previously,¹ highlights are included below. Other environmental exposures that aggravate the severity and persistence of asthma symptoms include ETS, air pollution (e.g., tobacco smoke, high levels of NO₂ and diesel fuel), stress, and dietary factors (vitamin D and fish oil).¹¹⁻¹⁸

Viral respiratory tract infections frequently interact with allergic inflammation in the airway to provoke attacks of asthma during childhood and into the adult years,¹⁹⁻²¹ and are most likely to cause attacks in those with exacerbation-prone asthma. Previous studies have shown that the relationship between viral infections and allergic inflammation in the pathogenesis of wheezing exacerbations changes with age.^{22, 23} During infancy, 90% of children who experience episodes of wheezing (bronchiolitis) test positive for viral infections,²³ and in the Northern hemisphere, most of these attacks occur during the mid-winter months when infections with RSV, but also influenza, and metapneumovirus, are prevalent.^{23, 24} Rhinovirus (RV) also causes wheezing in infancy and is the dominant viral pathogen causing exacerbations during the non-winter months.^{23, 25, 26} Finally, allergen exposure increases the risk of exacerbations of asthma in sensitized individuals.^{23, 27}

The discovery of the previously unrecognized RV-C species significantly improved our understanding for the pathogenicity of RV.²⁸ At least 160 RV types have been identified that are classified into 3 species (RV-A, RV-B, and RV-C). RV-A and RV-C are more likely to cause asthma exacerbations, whereas RV-B types are generally associated with mild disease.^{29, 30} RV-C infections appear to be more strongly associated with severe attacks of asthma and admission to intensive care for respiratory compromise.^{20, 31, 32}

Evidence from a variety of clinical and experimental studies suggest that some forms of asthma are associated with increased susceptibility to viral infections.³³ Clearly, asthma is associated

with a greater risk of developing airway obstruction and respiratory distress during infections with RV.³⁴ In addition, several *ex vivo* studies have demonstrated that RV infection of cultured epithelial cells from allergic asthmatics exhibit a reduced innate antiviral response and increased viral replication compared to cells from healthy non-asthmatic individuals^{35, 36} There are several mechanisms for type 2 airway inflammation to reduce antiviral responses, including suppression of antiviral responses by cytokines such as IL-13, antigen-induced cross-linking FcER1 receptors on plasmacytoid dendritic cells and monocytes, and overexpression of transcription factors that dampen antiviral responses.³⁷⁻³⁹ On the other hand, some experimental inoculation studies^{40, 41} and clinical studies^{42, 43} have found similar viral shedding in patients with asthma compared to nonasthmatic controls, suggesting that antiviral responses in asthma vary with disease severity, control or phenotype (e.g atopic vs. nonatopic). Finally, there is evidence that the timing and magnitude of interferon responses are important; brisk responses during the first hours of infection could inhibit viral replication and preclude severe illness, while weak initial responses could lead to greater replication and induction of high level interferon that contributes to symptoms of illness.^{44, 45}

In keeping with the hygiene hypothesis, exposure to microbial organisms (other than viruses) in the environment, or as part of the microbiota on our skin and mucosal surfaces, can influence immune responses to viruses and allergens. These exposures can decrease the risk for acute recurrent wheezing episodes in young children growing up on traditional European dairy farms or in inner-city home environments.^{46, 47} Whether probiotic treatments can be developed to mimic these effects is of interest. Additionally, pathogenic bacteria (*Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenza*) are more likely to be detected in wheezing infants⁴⁸ and during RV-induced exacerbations of asthma.^{29, 49} Among children with asthma, nasal microbiotas dominated by *Moraxella* were associated with an increased exacerbation risk.⁵⁰ Whether these microbiome signatures are also predictive of exacerbation frequency or

severity in adults is unclear. Future work is needed in terms of whether these signatures could help tailor exacerbation management strategies, including the selective use of antibiotics as a prednisone sparing option.

Personal Risks

Established biomarkers: eosinophils, IgE and FeNO. Eosinophils and in particular sputum eosinophils have been associated with exacerbations of asthma⁵¹ irrespective of whether the exacerbation was triggered by respiratory viral infections or inadequate treatment. This is substantiated by improvement with corticosteroids⁵² or more specific anti-eosinophilic biologics targeting the IL-5-IL-5 receptor axis, resulting in attenuated eosinophilic inflammation and less exacerbations.^{53, 54} As a predictor, higher blood eosinophil counts were associated with exacerbation prone asthma in some;^{6, 55, 56 57} but not in all studies.^{58, 59} Although Denlinger *et al*⁶ found a positive relation between sputum eosinophils and number of exacerbations in an unadjusted regression model, mean sputum eosinophil counts were not different between asthma patients with few exacerbations ($\leq 2/\text{p.a.}$) or exacerbation-prone ($\geq 3/\text{p.a.}$) asthma.^{6, 60} In several other studies, sputum eosinophils were not helpful to identify exacerbation-prone asthma⁵⁷, severe asthma⁶¹ or tobacco-naïve asthma patients⁵⁶. It is possible that sputum eosinophils in exacerbation-prone asthma patients are underestimated as they may have been activated to release their granular contents as a consequence of which they are not counted as eosinophils. This has been demonstrated with ongoing subepithelial deposition of eosinophil peroxidase despite mepolizumab-induced reduction of airway eosinophils.⁶² Likewise, it has recently been recognized that eosinophils can release their DNA as extracellular traps,⁶³ with a similar consequence.

DNA-extracellular traps are conventionally associated with neutrophils, can be induced in bovine and human pre-clinical models of respiratory virus infection, and have been shown to promote

subsequent T2 inflammation.^{64, 65} They can be detected in BAL samples from children with respiratory failure requiring mechanical ventilation with concomitant infection by RSV.⁶⁴ Whether they persist in the airway at baseline is unclear, and sputum neutrophils have not been associated with exacerbation proneness. By contrast, blood neutrophils may be a useful biomarker in select subsets of severe asthma, namely former smokers or obese patients with metabolic dysfunction.^{56, 66}

Together this suggests that high blood eosinophil counts, and possibly circulating neutrophil counts in select patient subsets, are useful and easily accessible parameters to distinguish exacerbation-prone asthma patients. The underrepresentation of the granulocytes in sputum is suggestive of their activation and future studies may be aimed at sputum markers of granulocyte activation (e.g. eosinophil cationic protein, myeloperoxidase, citrullinated histone H3), potentially having a greater discriminatory power to recognize exacerbation-prone asthma.

IgE, like eosinophils also associated with Th2 inflammation, has been proposed to drive exacerbations. In children with asthma, there is a close relationship between allergic sensitization and the risk of exacerbations. Children who are sensitized to multiple allergens at an early age are at greatest risk for exacerbations leading to hospitalization.⁶⁷ Allergy is also a major risk factor for exacerbations in urban children, especially if they are sensitized and exposed to indoor allergens such as cockroach and mouse.⁶⁸ A recent interventional study demonstrated that treating urban asthmatic children with omalizumab, which neutralizes IgE, reduces fall exacerbations, which are predominantly associated with rhinovirus (RV) infections.⁶⁹ Interestingly, omalizumab treatment also increased monocyte and dendritic cell interferon responses to RV⁷⁰⁻⁷², and reduced the number of RV infections and illnesses. These studies provide direct evidence that IgE-related mechanisms dampen antiviral interferon responses and increase susceptibility to RV infections and exacerbations. However, systemic

IgE was significantly reduced in adults with exacerbation-prone asthma.⁶ As the reduced systemic levels of IgE were not confirmed in a validation cohort, the jury is still out on the use of systemic or local IgE as a marker of exacerbation-prone asthma in adults.

Exhaled nitric oxide levels have been associated with exacerbation prone asthma, particularly in patients who also smoke.⁶⁰ This biomarker is driven by airway epithelial expression of inducible nitric oxide synthase, a gene in the top-10 list of those induced by IL13 stimulation.⁷³ In patients with severe asthma, high levels of FeNO may reflect differences in arginine metabolism and less efficient energy utilization,⁷⁴ which has been hypothesized to be modifiable with ketogenic diets. Notably, patients with elevated FeNO levels at baseline have a dupilumab-associated reduction in exacerbations, whereas patients with levels < 25 ppb have a treatment effect that does not differ from placebo.⁷⁵ Given that FeNO is usually suppressed by ICS, high levels of this biomarker despite adherence to this class of therapy could identify patients with high levels of IL13 expression and candidacy for response to dupilumab.

Genetics. Exacerbations have been an understudied phenotype for genetic analyses. Early candidate gene-by-environment approaches identified *P2RX7* as a risk for frequent exacerbations, with replication in other cohorts.^{76, 77} Subsequent genome-wide association studies (GWAS) have identified a large number of genes that are associated with asthma exacerbations, recently reviewed in.⁷⁰ To the best of our knowledge only in a Danish GWAS study, five susceptibility loci for recurrent severe exacerbations in early childhood asthma were identified and replicated in another cohort.⁷⁸ Four of these were already known as asthma susceptibility loci: *GSDMB*, *IL-33*, *RAD50* and *IL1RL1*. Of these *IL-33* and *IL1RL1*, encoding for the alarmin IL-33 and its receptor ST2 respectively, have been linked to (experimental) asthma exacerbations.⁷⁹⁻⁸¹ Although it appears that a splice variant of *IL-33* mRNA is responsible for asthma pathophysiology,⁸² it is not known as yet whether one of the *IL-33* polymorphisms can

be linked to the production of this splice variant, although other mechanisms leading to alternative splicing cannot be ruled out. So far, both *IL-33* and *IL1RL1* polymorphisms have been associated with Th2-driven responses,^{82, 83} but not yet with exacerbations, let alone exacerbation-prone asthma. A new susceptibility locus identified in the Danish GWAS study was Cadherin-related family member 3 (*CDHR3*).⁷⁸ The polymorphism rs6967330 in *CDHR3* resulted in an enhanced cell surface expression of the receptor for rhinovirus C (RV-C), which has been associated with frequent severe exacerbations in children.⁸⁴ This same polymorphism increases the risk for infections with RV-C, but not other respiratory viruses.⁸⁵ Besides the susceptibility loci for recurrent severe exacerbations it is possible that other genes associated with exacerbations are potential candidates for identifying exacerbation-prone asthma.

Comorbid conditions and diversity of asthma phenotypes. There is considerable consensus on comorbid conditions that relate to exacerbation-prone asthma. Multiple studies have identified higher body mass index,^{6, 55, 58} gastroesophageal reflux disease,^{6, 55, 86} (rhino)sinusitis,^{6, 55, 58, 86} smoking^{55, 60} and psychological problems^{18, 55, 86} as risk factors for frequent exacerbations. Many of these conditions also contribute to vocal cord dysfunction, which has independently been associated with frequent exacerbations,⁸⁷⁻⁸⁹ and may become acutely symptomatic more quickly than the traditional natural history of 3 to 5 days^{90, 91} Obviously, these significant findings were obtained in relatively large cohorts and thus these clinical parameters may not be equally predictive at the individual level. Therefore, it may be of interest to study these parameters in a prospective study to test their predictive value.

Although bronchodilator responsiveness (BDR) and mucus hypersecretion are cardinal features of asthma, there is tremendous diversity in these phenotypes in patients with severe disease that has not yet been targeted for biomarker-driven therapeutic intervention.^{6, 92} For example, the range of maximum BDR in the SARP cohort was -9 to 58% for adults and -5 to 48% for

children in terms of the absolute difference between post- and pre-bronchodilator measurements. There was a direct relationship between BDR and exacerbations across the ages; the rate ratio was 1.2 (95% CI 1.1-1.4, $p < 0.001$) for every 10% difference in BDR, even after adjustment for blood eosinophils, sinusitis, GERD and BMI (Figure 1).⁶ At present, there are no studies using BDR to predict responsiveness to add on therapy, although it stands to reason that this might be a good biomarker for use of LAMAs. Similar diversity exists for mucus plugs identified on high resolution chest CT scans: 59 of 139 participants (42%) studied in this subset had no mucus plugs, 44 (32%) had plugs in fewer than 4 airway segments, and 36 (26%) had plugs in 4 or more segments.⁹² Although the study was underpowered for exacerbations, these categories were strongly associated with decrements in postbronchodilator lung function. Sputum eosinophils and expression of IL13 and IL5 mRNA were associated with these mucus scores. Mechanistic experiments in this study demonstrate that eosinophil peroxidase contributes to thiol-crosslinking necessary for the formation of plugs (Figure 2).⁹² Future work is needed to automate the detection of these plugs (primarily located in smaller airways) before this biomarker is ready for clinical practice, but it is hypothesized that this may be another indicator for responsiveness to IL5-, IL5R-, or IL4R α -directed biologic therapies.

Emerging biomarkers. Apart from the biomarkers mentioned above, several others were identified that relate to frequent exacerbations. Thymic stromal lymphopoietin (TSLP) was originally discovered as one of the asthma susceptibility loci for asthma. Corren *et al*⁹³ showed that anti-TSLP reduced the exacerbation rate in uncontrolled asthma despite optimal treatment with inhaled corticosteroids and LABAs. Anti-TSLP particularly attenuated Th2 responses. As TSLP is produced predominantly by bronchial epithelial cells it can therefore be assessed in sputum or bronchoalveolar lavage only, which limits its use as a biomarker.

There are few biomarkers of exacerbation-prone asthma with neutrophilic inflammation. Systemic inflammation may be driven by IL-6, associated with neutrophils and lower lung function and more frequent exacerbations in the SARP cohort.⁶⁶ IL-17F, which was detectable in both the bronchial and nasal mucosa, was recently identified as a marker of a frequent exacerbator asthma endotype.⁹⁴ Even more interesting is the chitinase-like protein, YKL-40, which was markedly enhanced systemically in a cluster of patients with late onset asthma with frequent exacerbations.⁹⁵ Like IL-17F (and IL17A), YKL-40 is associated with neutrophilic inflammation and it would be of interest to see to what extent these biomarkers correlate with each other in neutrophilic asthma. These pathways may be more likely to be resistant to corticosteroids. Exacerbation prone subsets in cohort studies have frequently been associated with use of higher doses of steroids, but data are lacking to establish a mechanistic connection between steroid resistance and exacerbations.

Management

The morbidity associated with exacerbation-prone asthma is considerable in terms of health care costs, anxiety and distress, missed work and school and risk of adverse outcomes such as hospitalization, intubation and even death. Although multiple studies demonstrate that good adherence to maintenance therapy helps prevent exacerbations^{96, 97}, it is not clear that participants with exacerbation prone asthma have poor adherence^{6, 60}, particularly in cohorts with a high level of corticosteroid resistance⁹⁸. The remainder of this review emphasizes the importance of prevention and treatment of acute asthma attacks even after adherence has been optimized.

Prevention

Therapies directed at baseline inflammation remain the best way to prevent exacerbations triggered by acute exposures, and the roles of patient centered management strategies and

monitoring devices are increasing in both prevalence and importance.^{99, 100} Unfortunately, biomarker identification of the best responders to ICS or LTRA has yet to reach clinical feasibility and practice.^{101, 102} Acknowledging a narrow incremental benefit at the highest doses of ICS, the 2019 GINA guidelines provide several useful recommendations for patients who remain poorly controlled despite medium dose ICS/LABA with or without a third controller such as an LTRA or theophylline. Use of high dose ICS/LABA should be restricted to 3-6 months, with a plan to revert to medium ICS/LABA plus an add-on option for patients who do not respond. These include tiotropium, maintenance dosing for azithromycin, biologic therapies directed at IgE, IL5, IL5R, or IL4Ra, bronchial thermoplasty; maintenance OCS should be considered a last resort. Most of these options have an approximate 50% response rate and aside from blood eosinophils, the predictive biomarkers associated with clinical responsiveness require further development.¹⁰³⁻¹⁰⁵

Evidence that allergen induced inflammation influences susceptibility to RV infections, illnesses and exacerbations of asthma has led to significant improvements in asthma management during childhood. Those with mild to mild-persistent asthma often have seasonal risks for exacerbations that correlate with allergen exposures that are known to vary in different geographic locations.¹⁰⁶ These children are likely to benefit from seasonal medication plans that optimize their use of medications during periods of increased allergen exposure. Those with moderate to severe disease and a history of multiple exacerbations are candidates for monoclonal antibody-based treatments (e.g., omalizumab, dupilumab, and mepolizumab) that block Th2-related pathways. For example, the administration of omalizumab to inhibit IgE-mediated pathways can reduce seasonal peaks of exacerbations among children with moderate to severe asthma, including those who test positive for RV (Figure 3).^{71, 107} The benefits of these treatments have been exciting. However, these treatments are not allergen specific and, once started, the challenge is to decide when these treatments can be stopped or weaned. Whether

the combination of these treatments and allergen specific immunotherapy would be preferable, and whether administering these medications early in childhood will have a disease modifying effect as asthmatic children grow older are questions of interest.

Age and consideration of phenotype can also influence the response to treatment. To identify phenotypes of wheezing and asthma, children 12-71 months of age with recurrent wheezing from five NIH-sponsored clinical trials were analyzed using latent class analysis.¹⁰⁸ Four classes were identified based on patterns of allergen sensitization or exposures (Figure 4). The association between treatment response to daily inhaled corticosteroid was assessed in participants in the Prevention of Early Asthma in Kids (PEAK) trial. The results showed that children in the sensitized and exposed to pets group (Class 2) and the multiple sensitization with eczema group (Class 4) had a beneficial response (reduction in wheezing episodes) to ICS, while there was no response in the other two groups. These findings suggest that assessment of allergic sensitization and environmental exposures may identify children more likely to benefit from ICS, and importantly, identify those children in whom alternate therapies are needed.

Acute episodes

The pathogenesis of acute exacerbations of asthma involves bronchospasm, often in airways with baseline narrowing due to remodeling, mucus plugging, and airway inflammation that can lead to hyperemia, shedding of cells into the airway, reduced epithelial barrier function and edema due to mast cell activation and capillary leakage. Despite many additional insights into the mechanisms of airway inflammation and obstruction, the cornerstones of therapy remain the use of bronchodilators and systemic corticosteroids. These provide satisfactory relief in most mild cases, but treatment failures are common and can lead to severe airway obstruction and respiratory arrest.

Inhaled β_2 -agonists such as albuterol are fast-acting and effective bronchodilators, however, they are less effective at relieving bronchospasm that is initiated by acute respiratory illness. In a classic study, Reddel and colleagues found that diurnal variability of PEF was increased during periods of poor asthma control, and normalized with regular use of ICS.¹⁰⁹ During exacerbations that were associated with clinical respiratory illness, PEF fell (without increasing diurnal variability) and responses to inhaled β_2 -agonist were impaired. These data suggest that during virus-induced exacerbations, airway edema, mucus plugging and shed cells may be more important than smooth muscle contraction in contributing to airway obstruction, and underlines the need to develop specific treatments for these pathologic processes.

For patients on daily low-dose ICS as a controller regimen, high-doses of inhaled corticosteroids have been used in “yellow-zone” plans in the hope that intervention at the early stages of worsening asthma would obviate the need for systemic steroid and reduce the probability of exacerbations of asthma. While early small-scale studies were supportive of this approach, well-designed studies in children and adults have definitely shown that quadrupling or quintupling the dose of ICS at the first sign of worsening asthma did not reduce the risk for exacerbation.¹¹⁰ Thus, this practice should be abandoned. In contrast, in children and adults with mild asthma that is not treated with daily ICS, intermittent use of high-dose ICS and albuterol in yellow zone plans can reduce the risk of exacerbations.¹¹¹⁻¹¹³

Treatment of acute wheezing in preschoolers prone to recurrent episodes remains problematic. Neither high-dose inhaled budesonide nor oral montelukast started at the first signs of acute respiratory illness reduced the subsequent need for oral corticosteroids. However, both treatments caused modest reductions in airway symptoms, especially in those children with positive asthma predictive indices.¹¹⁴ Two randomized clinical trials found that early initiation of azithromycin at the first sign of respiratory illness reduced subsequent wheezing and need for

OCS.^{115, 116} This effect did not seem to be related to the type of bacteria in airway secretions.¹¹⁷

However, there are concerns about adverse effects of widespread use of antibiotics in children with respiratory illnesses. In addition, a recent clinical trial evaluated the efficacy of azithromycin in preschoolers who presented to the emergency department with acute wheezing illnesses.¹¹⁸ In this study, azithromycin failed to shorten either duration of the acute wheezing episode, or time to the next wheezing episode.

Finally for all patients with asthma, it is important to teach patients about two major signs of poor control, which include night-time or exercise-induced symptoms (summarized in the 2019 GINA guidelines, <https://ginasthma.org/severeasthma/>). These symptoms warrant adjustments in asthma management and/or closer attention to medication compliance, especially in children. Clinic visits planned when these symptoms are present, or prior to risk seasons (e.g., before children start the school year) may be fruitful to monitor adherence and inhaler technique.

Vision for Future Treatments:

One of the key features of acute exacerbations is mucus plugging, leading to airway obstruction and closure. Of the various mucin proteins, overproduction of MUC5AC has been closely linked to acute severe exacerbations of asthma and a phenotype of severe treatment-resistant asthma in adults. Type 2 inflammation mediated by cytokines such as IL-13 and IL-4 can induce goblet cell metaplasia and MUC5AC production. Infections with respiratory viruses can exert similar effects, but appear to do so through alternate mechanisms that are independent and perhaps additive with type 2 inflammation. New approaches to treatment of mucus overproduction could have clinical utility in treating exacerbation-prone asthma as well as other chronic airway diseases such as COPD.¹¹⁹

As alluded to previously NETosis of airway neutrophils is a form of cell death, and the shed DNA can serve to trap and immobilize pathogens as a mechanism of host defense. However, viral respiratory infections can induce large scale NETosis that can in turn promote type 2 airway inflammation and airway obstruction.⁶⁵ In mouse models, aerosolized delivery of DNase can help to relieve virus-induced airway obstruction. DNase is also used in the treatment of cystic fibrosis to improve lung function and reduce exacerbations.¹²⁰ Whether this approach has merit in acute asthma is under investigation.

Another potential approach to treating exacerbations could be to target airway pathogens that have been implicated in their pathogenesis. There have been long-standing efforts to develop antiviral agents that inhibit RV replication, and new inhibitors continue to be evaluated.^{121, 122} In addition, there are efforts to develop innate immune stimulators that boost resistance to multiple respiratory viruses. Finally, there are ongoing programs to develop RV vaccines based on either targeting of shared epitopes or a multiplex approach.^{123, 124} Vaccines targeting bacterial pathogens such as *Moraxella catarrhalis* could also be useful approaches to reducing the risk for exacerbations as well as respiratory infections.

Conclusions

Exacerbations account for much of the morbidity and cost associated with chronic asthma, and new preventive and treatment approaches are needed. Insights into the immunopathogenesis of asthma have led to new biologics that have proven efficacy in reducing the risk for exacerbations in patients with moderate to severe asthma. While these developments represent progress in preventing exacerbations, remaining knowledge gaps include developing an evidence base to determine which medication will work best for any given patient. New initiatives toward understanding different phenotypes of asthma, including those associated with repeated exacerbations, may lead to greater precision in treatment. There are also important

obstacles related to cost, the use of biologics in children, and prevention of exacerbations in patients with type-2-low asthma phenotypes. In addition, better understanding the contributions of airway viruses and bacteria to exacerbations will lead to new strategies for prevention. Unfortunately, there has been less progress in developing new treatments for exacerbations during the acute illness. Evidence implicating mucin hypersecretion and airway inflammatory responses from both infectious and noninfectious sources could lead to new approaches toward achieving this goal.

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Legends:

Figure 1. Relationship between bronchodilator reversibility and exacerbation rates. Among children and adults participating in the Severe Asthma Research Program, maximum post-albuterol reversibility was related to exacerbation rates (95% confidence interval, multivariable negative binomial model). Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.⁶

Figure 2. Contribution of eosinophil peroxidase to mucus plug formation. When airway eosinophils are activated by inflammatory stimuli in the airway, eosinophil peroxidases catalyze a reaction in which H₂O₂ and thiocyanate (SCN⁻, from plasma) form hypothiocyanous acids (HOSCN). In turn, HOSCH can cross-link thiol groups on strands of mucin released from goblet cell. The cross-linked mucins are quite viscous, and can form plugs that obstruct lower airways⁹². This figure has been reproduced with permission.

Figure 3. Omalizumab reduces seasonal exacerbations. Seasonal rates of exacerbations (95% confidence intervals) are depicted for school-aged children participating in the Inner-City Anti-IgE Therapy for Asthma (ICATA) Study. Children were randomized to guidelines-based treatment ("placebo") or guidelines-based treatment together with omalizumab. [New England Journal of Medicine, Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al, Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children, Volume 364, Pages 1005-15. Copyright © (2011) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.¹⁰⁷

Figure 4. Early childhood wheezing phenotype and the response to inhaled corticosteroid. Data from five NIH-funded treatment studies were combined, and four classes of early childhood

844 recurrent wheeze were identified by latent class analysis.¹⁰⁸ In the PEAK (Prevention of Early
845 Asthma in Kids) study, exacerbation rates in children treated with placebo (solid bars) and daily
846 ICS (hatched bars) are depicted for each class. This figure has been reproduced with
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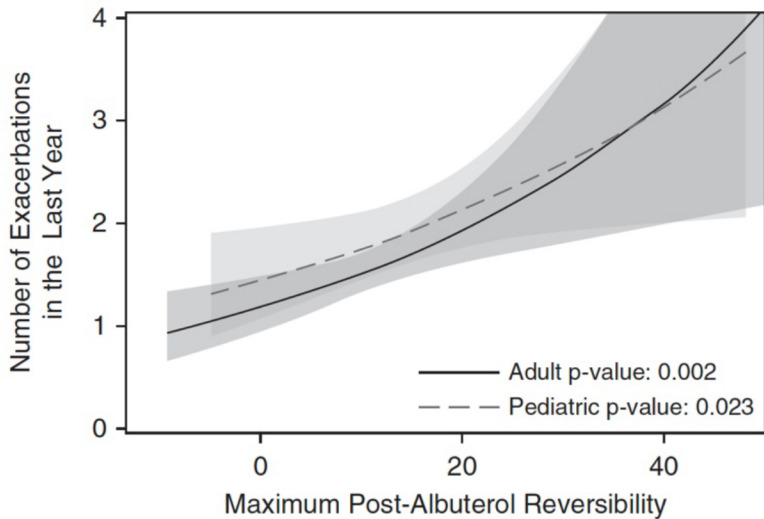


Figure 1.

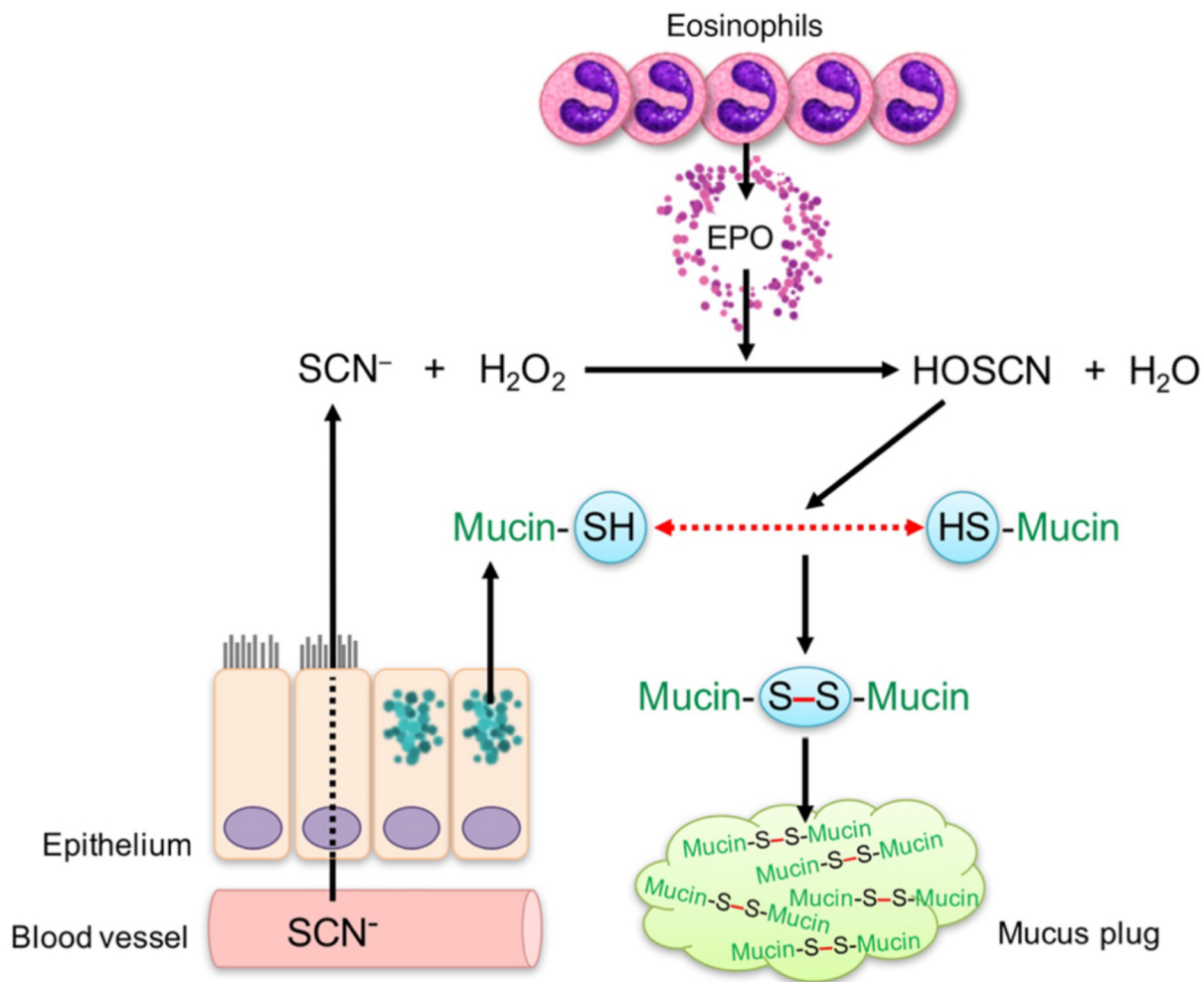


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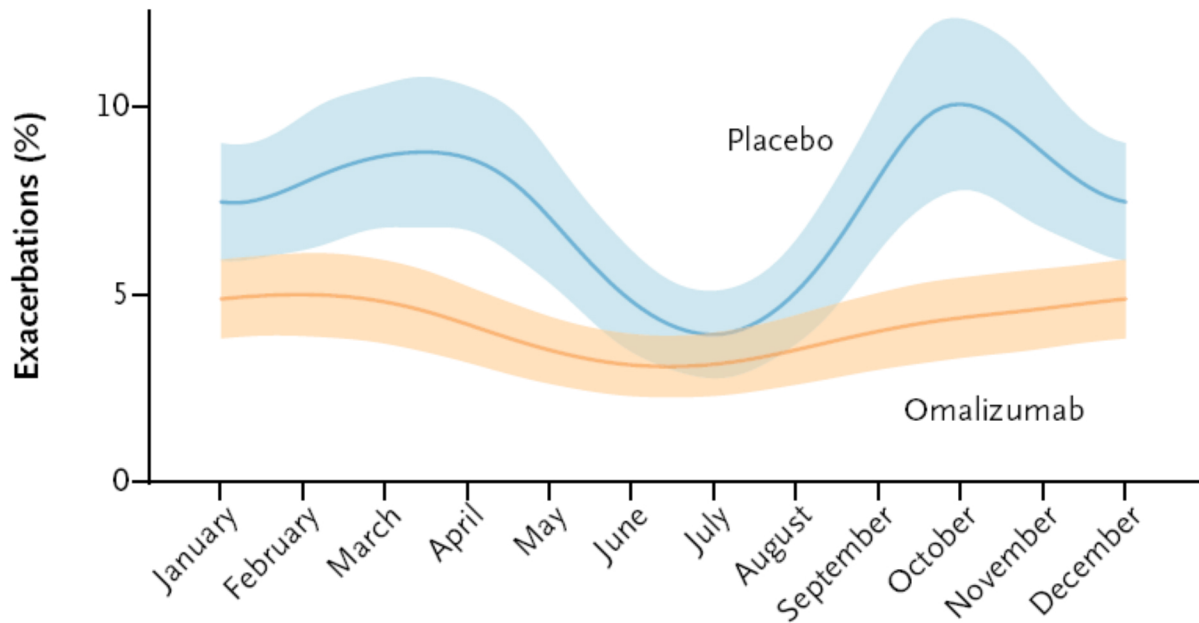
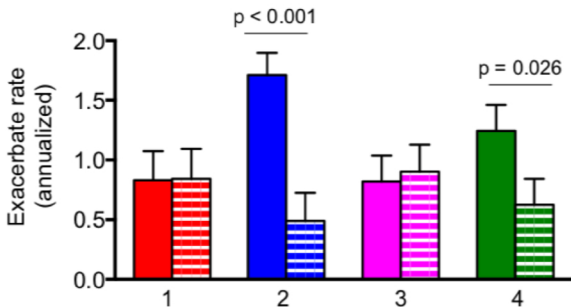


Figure 3.



Class	Defining Features
1	Minimal sensitization
2	Sensitization with indoor pet exposure
3	Sensitization with tobacco smoke exposure
4	Multiple sensitization with eczema

Figure 4.

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Thank you very much,
Dawn

--

Dawn Angel

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