Consequences of severe asthma exacerbations

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Purpose of review
Asthma exacerbations are major factors in asthma morbidity and also have long-term consequences.

Recent findings
Asthma is characterized by an accelerated and progressive loss of lung function. Recent evidence has pointed to the frequency of exacerbations as being a significant contributor to a loss of lung function in asthma.

Summary
A consequence of asthma exacerbations is a greater loss of lung function. Airway inflammation is central to asthma severity and susceptibility for exacerbations. Evidence suggests that the increase in airway inflammation during an asthma exacerbation further compromised lung function. Treatment of severe asthma with Type (T)-2 directed biologics significantly prevents the frequency of exacerbations in severe asthma. Early indications also suggest that prevention of exacerbations by biologics may reduce a loss in lung function from exacerbations.

Keywords
airway inflammation, biologics, exacerbations, loss of lung function

INTRODUCTION

Exacerbations contribute to the morbidity and overall disease burden of asthma [1,2▪]. Acute exacerbations are an emergency and require immediate efforts to resolve compromised airflow obstruction [3▪]. Although asthma attacks are dramatic events for patients and families, their influence on asthma does not end with a resolution of the acute event. In some patients, exacerbations lead to long-term consequences that fundamentally change the underlying pathophysiology of asthma. The objective of this review is to examine the consequences of exacerbations in asthma in relationship to an accelerated loss of lung function, mechanisms contributing to a loss of lung function and therapeutic options to modify the consequences of exacerbations in asthma.

EXACERBATIONS PROVOKE INFLAMMATION IN ASTHMA

Although exacerbations can occur in any patient with asthma, the primary at-risk phenotype is severe asthma [4]. Airway inflammation is most intense in severe asthma and least responsive to high-dose treatment [5–8]. Most patients with severe asthma have Type (T) 2 inflammation, which is characterized and driven by overexpression of interleukin (IL)-4, IL-5 and IL-13 [9▪▪,10▪▪,11]. Biomarkers denoting T2 asthma include elevated blood eosinophils, FeNO and IgE [12▪]. These associations suggest that the inflammatory features of severe asthma are susceptible or conducive to exacerbations and contribute to adverse consequences with exacerbations.

Many environmental factors contribute to exacerbations in susceptible or at-risk asthma hosts. However, viral respiratory infections are the predominant cause of exacerbations with rhinoviruses far and away the greatest provoker [13]. Rhinoviruses infect the lower airways epithelium to set into motion increased airway inflammation beginning with the generation of alarmins, including IL-33, IL-25 and TSLP. IL-33 activates ILC2 cells to generate IL-5 and IL-13, which, in turn, promote eosinophil production and migration to the airway to further existing inflammation [14]. Neutrophils also contribute; rhinovirus causes NETosis and the release of double-stranded DNA to activate Th2 cells and generate IL-4, IL-5 and IL-13 [15,16]. The accentuation of existing T2 inflammation by rhinovirus compromises airflow.

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KEY POINTS

- Asthma exacerbations are major factors in disease morbidity, and this includes long-term consequences of accelerated loss of lung function.
- Respiratory tract infections with rhinoviruses are the major cause of exacerbations. Rhinoviruses infect the lower airway and provoke T2 inflammation to compromise lung function and to possibly set into motion accelerated loss of lung function.
- Biomarkers of T2 inflammation, eosinophils and FeNO, identify patients who are at the greatest risk for exacerbations.
- Emerging evidence with T2 inflammation directed biologics has shown striking effectiveness in preventing exacerbations in severe asthma. Whether prevention of exacerbations will alter lung function loss needs to be established.

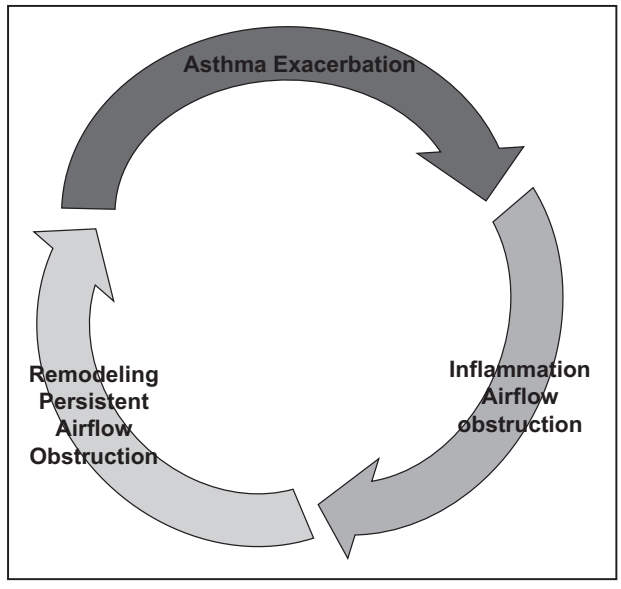

FIGURE 1. The vicious cycle of asthma exacerbations. Asthma exacerbations provoke an acute inflammatory response, which includes eosinophils and other Type 2 pathway activation. These responses cause airway obstruction and acute symptoms of an exacerbation. The acute inflammatory responses are followed by activation of airway remodelling with more persistent airflow obstruction. Low lung functions are a risk factor for exacerbation and participate in creating a vicious cycle of recurring airway injury and loss of lung function.

The complexity of inflammation associated with exacerbations is reflected by the multiple, interacting transcriptomic pathways and genes expressed [17]. The infectious-driven modules generated with an exacerbation include epithelial cell dysfunction, extra-matrix production and mucus formation along with components of T2 inflammation. Collectively, these rhinoviruses -provoked inflammatory reactions cause acute airflow obstruction and initiate airway remodelling to promote a progressive loss of lung function.

Host factors identify those most at risk for exacerbations. Most dominant and important is a past history of exacerbations [12▪]. Biomarkers for T2 inflammation, elevated FeNO and eosinophils, also earmark at-risk patients [3▪,12▪]. Finally, reduced lung functions are associated with more frequent exacerbations [18]. This latter scenario suggests a vicious cycle (Fig. 1). Asthma exacerbations cause a greater risk for the loss of lung function, lower lung function is a risk for an exacerbation, and the cycle becomes perpetuated with each exacerbation. In severe asthma, increased blood eosinophils and/or FeNO identify not only the presence of T2 inflammation but also the risks for exacerbations. Collectively, these data suggest that exacerbations drive existing T2 inflammation to further compromise airway inflammation, structure and function.

EXACERBATIONS ACCELERATE A LOSS OF LUNG FUNCTION

Asthma is associated with an accelerated and progressive loss of lung function [19]. The loss of lung function is variable amongst asthma patients. To address the hypothesis that severe exacerbations contribute to a loss of lung function, Bai *et al.* [20] analysed historical information from a nonsmoking cohort of 93 moderate-to-severe asthma patients who had not received inhaled corticosteroid (ICS). In the 47 patients who had a history of severe exacerbations, there was a significantly lower percentage predicted FEV_1 ($66\% \pm 19$ vs. $78\% \pm 17\%$, $P = 0.002$) compared with 'nonexacerbators' over an 11-year observation.

In a 3-year perspective study, Matsunaga *et al.* [21] found the frequency of exacerbations to accelerate the loss of lung function correlated with the annual decline in lung function. Furthermore, exacerbations were associated with increases in airway hyperresponsiveness (AHR) and correlated with declines in lung function. On the basis of exacerbation-associated increases in AHR, the investigators postulated that an enhanced loss of lung function reflected heightened and persistent inflammation from the exacerbation. Matsunaga *et al.* [21] suggest that increased airway inflammation from exacerbations is central to a loss of lung function.

TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens)

represents a large observational prospective cohort ($n = 2429$) and an opportunity to analyse the effects of severe or difficult-to-treat asthma on underlying characteristics of disease [22]. Over 3 years of observation, the annual decline (i.e. percent predicted FEV_1) in lung function was greater in patients with exacerbations (1.97% predicted ± 0.36%, $P < 0.001$). These differences were noted at all age groups, but most pronounced in children (3.13% predicted ± 1.01%, $P = 0.003$), possibly representing a period of more rapid lung growth and susceptibility to the adverse effects of exacerbations.

Soremekun *et al.* [23▪▪] used a broad based asthma population from the Optimum Patient Research Data that included 109 182 patients with follow-up information ranging from 5 to 50 years. Peak expiratory flow (PEF) was the primary pulmonary function outcome. Key data found a progressively greater fall in lung function with increasing annual rates of exacerbations. Although the decline in lung function was greater in the 18–24 year age group, lung function decline also occurred in older individuals with lower lung function at baseline. The authors suggested that the observations in older patients with asthma reflect a persistent deteriorating phenotype.

The NHLBI Severe Asthma Research Program (SARP) was established to identify the characteristics and mechanisms of severe asthma. On the basis of physiologic, inflammatory and comorbidity features, an analysis of 709 individuals in SARP-3 identified features of exacerbation-prone asthma (EPA) [18]. For 1 year prior to an analysis, 294 individuals had no exacerbations, 242 had few (one to two) and 173 had three or more exacerbations. Lung functions were lower in relationship to the frequency of exacerbations with the following risk factors identified: sputum eosinophils in adults ($P = 0.028$), a trend with absolute blood eosinophils ($P = 0.056$), sinusitis and increased BMI; the increase in eosinophils represents a T2 inflammatory phenotype.

To gain further insight into patterns of exacerbation-associated altered lung function, SARP individuals were given a single 40 mg injectable dose of triamcinolone [24▪▪,25]. The changes in lung function reflected corticosteroid responsiveness. Following the corticosteroid injection, SARP individuals were followed for 2 years to determine the trajectory of lung function changes: improvement, no change, mild decline or severe decline. SARP individuals with a severe decline in lung function also had a greater cumulative frequency of exacerbations, suggesting that recurrent exacerbations contribute to a progressive loss of lung function rather than one-time insults.

MECHANISMS CONTRIBUTING TO A DECLINE IN LUNG FUNCTION

Eosinophils are a biomarker for risks of exacerbation, contribute to airway inflammation and are a proven interventional target to diminish risks of exacerbations [26,27]. Moreover, with progressively greater levels of peripheral blood eosinophils, for example 150–500 cells/μl, risks for exacerbation increase but so does the prevention of exacerbations by mepolizumab [28–30]. To further determine the possible relationships of eosinophils to exacerbation associated declines in lung function [31], Ortega *et al.* [30] analysed data from DREAM [29] and MENSA [30]. A total of 1192 individuals had received either placebo or mepolizumab in these studies. Individuals who did not experience exacerbation with mepolizumab treatment had improvement of their postbronchodilator FEV_1 (143 ml), whereas patients with three or more exacerbations had a mean adjusted decline of -77 ml. From modelling analyses, it was determined that each exacerbation led to a decrease of 50 ml in lung function, suggesting that adverse effects of exacerbations on lung function are cumulative. Mepolizumab reduced eosinophils and the frequency of exacerbations to suggest a contributing role for eosinophils in exacerbations on lung function loss.

Many factors contribute to airflow obstruction in asthma including occlusion of the airways by mucus plugs. Multidetector computed tomography (MDCT) lung scans were used to detect the presence of mucus plugs [32]. Mucus plugs were detected in 58% of asthma individuals vs. 4.5% of controls. In individuals with high mucus plug scores, sputum eosinophils were greater, IL-5 was increased and the MUC5AC:MUC5B ratio shifted to an overexpression of MUC5AC. There was a significant correlation between sputum eosinophils and mucus score. Sputum eosinophil peroxidase (EPO), reflecting eosinophil activation, was greatest in high mucus score individuals. Finally, in-vitro modelling suggested that activation of eosinophils and generation of EPO changed the rheology of mucin into mucus plugs. MUC5AC overexpression may also be an important regulator of mucus production, formation of mucus plugs and diminished lung function.

To gain greater insight into the characteristics of mucus plugs in asthma, Tang *et al.* [33▪] repeated MDCT lung scans 3 years later in 164 participants from the original observations by Dunican *et al.* [32]. Fifty-three percent of the participants had the same mucus plug score 3 years later. Furthermore, airway segments with mucus plugs at baseline tended to have mucus plugs present in the same areas. Finally, and in relation to the consequences of exacerbations, patients with persistent mucus plugs had

greater annualized exacerbation rates and resembled the previously described EPA phenotype [18]. Finally, increases in mucus scores correlated with increases in blood ($r = 042$, $P < 0.001$) and sputum ($r = 0.39$, $P < 0.001$) eosinophils to further suggest a causative association with eosinophils, T2-inflammation and airway obstruction.

Declines in lung function are acquired and likely relate to the frequency of insults from exacerbations. To gain insights into possible genetic factors that account for the loss of lung function, Shrine *et al.* [34] conducted a genome-wide association study using two large asthma and control cohorts. Three novel SNPs were identified in the MUC5AC region in individuals with moderate-to-severe asthma and airflow obstruction, but not in mild asthma. The authors note that severe asthma is characterized by increased medication use, decreased lung function and more frequent exacerbations [7]; therefore, one factor contributing to severe asthma includes an overexpression of MUC5AC alleles, which may account for increased airway mucus, mucus plugs and diminished lung function.

The URECA (Urban Environment and Childhood Asthma) birth cohort includes children from high-risk urban areas and was established to identify risk factors for asthma [35]. At age 10 years, six patterns or phenotypes of disease emerged in URECA when clustered by atopy and wheeze [36▪▪]. Of particular interest to our discussions is the High Wheeze/High Atopy/Low Lung Function (HW/HA/LF) cluster. Nasal epithelial cells were used to identify transcriptomic modules in these clusters. Two gene modules were identified only in the HW/HA/LF group: IL-13 and MUC5AC. As the authors note, these findings demonstrate an overexpression of aberrant molecular pathways, which include dysfunction of secretory and ciliated epithelial cells as well as epithelial mast cells. HW/HA/LF was also linked to a decreased expression of three modules including a large set of type I/III interferon inducible genes, which may indicate diminished viral immune responses in asthma as noted by others [37–39]. Collectively, these results suggest epithelial injury and mucus hypersecretion in the presence of an antiviral deficiency as contributors to exacerbations and associated loss of lung function (Fig. 2).

ASTHMA TREATMENT: EFFECTS ON THE CONSEQUENCES OF EXACERBATIONS AND PREVENTION OF ADVERSE FROM SYSTEMIC CORTICOSTEROIDS

Airway inflammation is hypothesized to increase risks for exacerbations and is a major contributor to progressive worsening of airflow obstruction. To test this hypothesis, O'Byrne and co-investigators of START (Inhaled Steroid Treatment vs. Regular

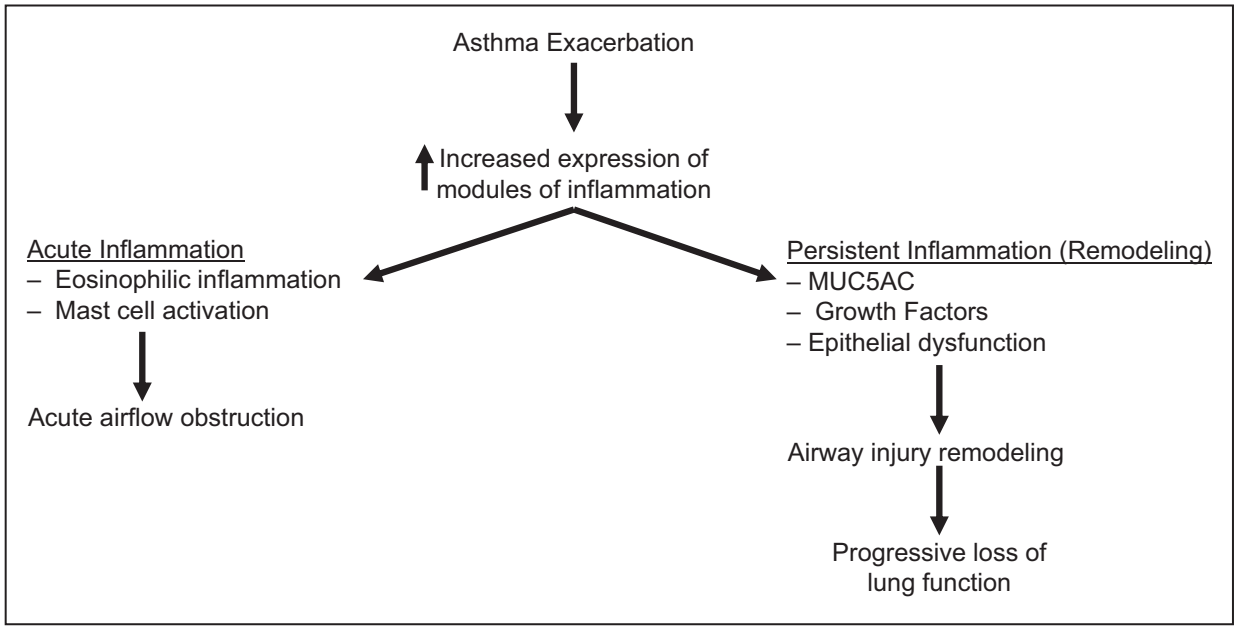

FIGURE 2. Mechanisms of rhinovirus provoked asthma exacerbation and pathways to progressive loss of lung function. An asthma exacerbation provokes multiple modules of inflammation. There is a rapid onset of acute inflammation that is driven by T2 inflammation including eosinophils. This leads to acute airflow obstruction and an increase in asthma symptoms. The acute response is followed by the activation of a variety of pathways that include mucus hypersecretion, airway injury, altered epithelial cell function and remodelling. Collectively, exacerbations lead to acute airflow obstruction followed by pathways regulating airway remodelling and accelerated loss of lung function.

Therapy in Early Asthma) [40] evaluated the effect of an early intervention with ICS on changes in pulmonary functions over 3 years and in relationship to exacerbations. START enrolled patients of all ages with recent onset asthma to test the hypothesis that early intervention with ICS prevents lung function loss during the initial years of diagnosis [41]. In the absence of ICS treatment, exacerbations were associated with a loss of lung function, which did not occur if ICS had been used. These data suggest that inflammation was diminished by ICS to prevent lung function decline with exacerbations.

Although ICS improve asthma control, their effectiveness in preventing a loss of pulmonary function is not consistent. In severe asthma, even high doses of ICS do not prevent exacerbations [5,42]. The available T2-directed biologics have specificity for components of inflammatory pathways contributing to exacerbations and may reduce or prevent lung function loss [10▪▪,43▪]. T2 biologics reduce eosinophilic inflammation by targeting IL-5 and IL-5R (mepolizumab, reslizumab and benralizumab) to reduce exacerbations by approximately 50% [30,44–46]. These findings suggest that reducing the availability of eosinophils is a significant, but not only, regulator of exacerbations.

Similar reductions in exacerbation are achieved by targeting the IL4/IL13 pathways with dupilumab [47]. In asthma patients with evidence of T2-inflammation, blood eosinophils more than 150 cells/μl or FeNO more than 25 ppb, exacerbations over a 52-week study were reduced by approximately 50%. Furthermore, dupilumab improved FEV_1 values. Although these data do not indicate that prevention of exacerbations relates to improved lung function, it is a reasonable conclusion.

TRAVERSE was an open-label, long-term study with dupilumab to evaluate its long-term safety [48▪▪]. TRAVERSE also provides insight into the prevention of exacerbations and effects on lung function. Individuals randomized to dupilumab in QUEST [47] continued on dupilumab for another year to provide a 2-year collective dosing of dupilumab. Key findings from TRAVERSE were a progressive reduction in exacerbation rates and sustained improvement of the FEV_1. These data support, but do not prove, that an ongoing control of exacerbations prevents risks for loss of lung function. There was also a rapid onset reduction of FeNO and gradual fall in blood eosinophils, both of which are biomarkers for T2 inflammation. A reduction in these biomarkers implies diminished airways inflammation, reduced risks for exacerbations and stabilization of lung function.

Systemic corticosteroids (SCS) are components of treatment for acute and severe asthma [3▪,49]. To gain disease control, a small segment of severe asthma patients require daily maintenance SCS. Acute and long-term side-effects from SCS are well appreciated [49]. Moreover, recent evidence indicates that the threshold for adverse events occurs when a 1.0 g lifetime dose of SCS is exceeded and leads to increased risks for metabolic, cardiovascular, infections and orthopaedic consequences; this association represents a treatment consequence of exacerbations. Treatment with T2-biologics prevents exacerbations and, as a consequence, the need for SCS [10▪▪]. Moreover, mepolizumab, benralizumab and dupilumab significantly reduce maintenance SCS doses and, in most situations, improve asthma outcomes despite reduced SCS [49–52]. Thus, the appropriate selection of patients and treatment with biologics can diminish corticosteroid-associated consequences from exacerbations [10▪▪].

A major step to prevent consequences of exacerbations is an identification of who is at risk and what may be the mechanisms of exacerbation driven airway inflammation. In addition to evaluating the effects of mepolizumab on exacerbations in 6 to 17-year-old urban asthma children, Jackson *et al.* [53▪▪] also collected nasal samples for transcriptomic assessments to identify exacerbation risks and effects of treatment on concurrent modules of inflammation. Mepolizumab prevented exacerbations by 27% over the 52-week study. Prevention of exacerbations was associated with suppression of the T-2 inflammatory transcriptomic pathways. However, exacerbations occurred in patients treated with mepolizumab; in patients in whom exacerbations were not prevented by mepolizumab, the T2 pathway was suppressed, but the epithelial pathway modules of inflammation had increased. These findings suggest that the regulation of exacerbated inflammation is complex, involves multiple genetic pathways and blockage of one contributor may result in a reciprocal increase in another pathway to cause airway inflammation and loss of lung function. To achieve a more comprehensive suppression of exacerbation-associated inflammation will require selective regulation of all the pathways that contribute to an exacerbation (Fig. 3). The technology and tools for this approach exist, but they need to be fully developed, applied and translated to patient care.

CONCLUSION

Asthma exacerbations are associated with an increased loss of lung function. This relationship is most apparent in patients with severe asthma and adds to the existing morbidity in this high-risk group of patients. Although the mechanisms underlying an increase in lung function loss with

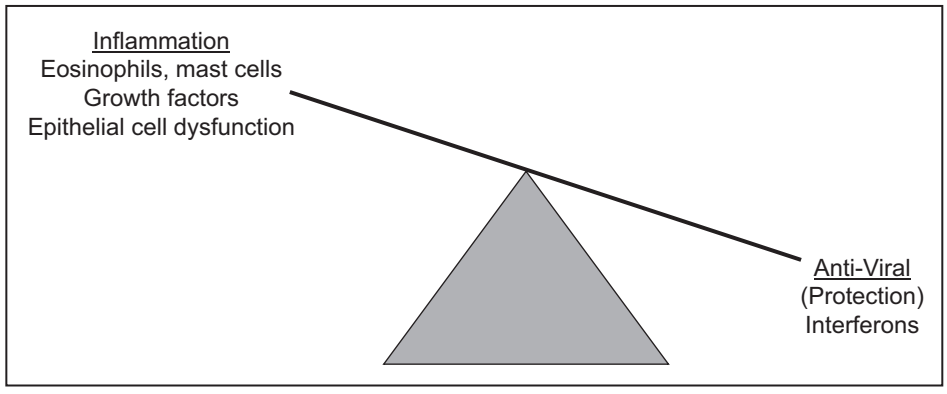

FIGURE 3. Characterization of an imbalance between inflammation and protection in asthma to create a risk for an exacerbation. Asthma is characterized by an imbalance that contributes to exacerbations. Exacerbations activate airway inflammation. However, there is evidence that asthma is also characterized by baseline defects in antiviral host defenses, including interferon expression. This imbalance explains, in part, the susceptibility of asthma for exacerbations and their consequences.

exacerbations have not been established, evidence is pointing towards increased airway inflammation, particularly T2 inflammation. In the high-risk, exacerbation-prone patient with asthma, conventional treatment with ICS-based approaches have not been effective in altering losses in lung function. In contrast, newly approved biologics are more effective in preventing exacerbations and may possibly prevent the accelerated loss of lung function.

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Conflicts of interest

W. W. Busse reports consultation and/or advisory board for Sanofi, Regeneron, GlaxoSmithKline, AstraZeneca, Genentech and Novartis.

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This is the first study to evaluate the efficacy of the anti-IL-5, mepolizumab, in children. In addition, airway transcriptomic analysis found that mepolizumab blocked eosinophil modules of inflammation to reduce exacerbations, but there was an increased expression of epithelial-derived inflammatory gene, which was associated with the appearance of exacerbations.