Published in final edited form as:

Ann Allergy Asthma Immunol. 2021 November ; 127(5): 524–529. doi:10.1016/j.anai.2021.08.014.

Inhaled Corticosteroids for the Prevention of Asthma Exacerbations

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Abstract

Objective: To provide an overview of the risk factors and mechanisms underlying asthma exacerbations and the role of inhaled corticosteroids in preventing exacerbations.

Data Sources: Queries for asthma exacerbations and inhaled corticosteroids were conducted using PubMed, searching for primary articles and reviews.

Study Selection: Studies written in English, with a focus on well-designed randomized controlled clinical trials.

Results: Asthma exacerbations remain a major source of morbidity, with future exacerbations most likely among patients with prior exacerbations and among those with peripheral blood eosinophilia. Exacerbations are often triggered by viral respiratory tract infections, but recent evidence support non-viral triggers as well. In terms of exacerbation prevention, several approaches to inhaled corticosteroid therapy have been demonstrated to be effective, including intermittent high dose ICS without use of background controller in preschool children with recurrent episodic wheezing, intermittent high dose ICS without use of background controller in adults with mild asthma, and as needed ICS dosing whenever rescue treatment is needed among children, adolescents, and adults with mild asthma not receiving daily controller therapy.

Conclusion: Inhaled corticosteroids are highly effective in preventing exacerbations of asthma. Multiple dosing strategies have been demonstrated to reduce exacerbation risk, allowing for a personalization of approaches based upon individual patient phenotypes and preferences.

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Disclosures:

Dr. Jackson reports personal fees from Novartis, GlaxoSmithKline, Sanofi, Regeneron, AstraZeneca, Vifor Pharma, and Pfizer
Dr. Bacharier reports personal fees from GlaxoSmithKline, Genentech/Novartis, Merck, DBV Technologies, Teva, Boehringer Ingelheim, AstraZeneca, WebMD/Medscape, Sanofi/Regeneron, Vectura, Circassia, royalties from Elsevier, personal fees from Kinaset and Vertex

Introduction

Asthma exacerbations are common events that lead to significant acute morbidity, resulting in frequent unscheduled health care visits and hospitalizations. These episodes can have a multitude of triggers with a set of common characteristics of airway obstruction leading to cough, wheeze and shortness of breath. Typically, exacerbations lead to prescriptions for systemic corticosteroids, which can have significant short and long-term adverse consequences(1, 2). Furthermore, there is growing evidence to suggest that asthma exacerbations can lead to progressive decline in lung function and worsened asthma severity over time.(3–5) Asthma exacerbations also represent an important example of health care disparities as they disproportionately impact minority children and adults living in underserved urban communities in the US.(6, 7) There has been increased focus over the past 2 decades on preventing asthma exacerbations. This review will focus on risk factors and mechanisms of exacerbations and the role of inhaled corticosteroids in their prevention.

Risk Factors and Mechanisms of Exacerbation Across the Ages

The first step in this process is to identify patients at greatest risk of exacerbation. Asthma exacerbations are most often triggered by viral respiratory infections, with rhinoviruses (RV) as the most frequent cause.(8) The strongest predictor of future exacerbations is a prior history of exacerbation.(9, 10) A post-hoc analysis in the Inner City Asthma Consortium (ICAC) identified differential risk factors in children based upon season of the year.(10) Low FEV_1/FVC ratio was associated with increased risk across all seasons. In contrast, type 2 inflammatory biomarkers such as fractional exhaled nitric oxide (FeNO) and peripheral blood eosinophils were significant risk factors for exacerbations in the summer and fall. The Severe Asthma Research Program (SARP) has also focused on exacerbation-prone asthma. Denlinger et al. identified higher blood eosinophils, elevated BMI, and greater bronchodilator response as significant risk factors for recurrent exacerbations.(11) Further, co-morbid conditions such as chronic sinus disease and gastroesophageal reflux were associated with increased exacerbation risk. Additional analyses in these cohorts has identified systemic inflammation, as assessed by IL-6, as an independent risk factor for exacerbations.(12–14)

The next step beyond identifying risk factors is to define mechanisms of asthma exacerbations. Much focus has been on the mechanisms of viral exacerbations, in part because the etiology of non-viral exacerbations has been enigmatic. A number of pathways have been identified in the pathogenesis of viral exacerbations of asthma. RV-induced activation of IL-33 has been shown to promote eosinophilic inflammation and asthma exacerbation in challenge-models in adults.(15) Denlinger et al. identified increased neutrophil burden in the lower airway in viral colds in adults that progress to exacerbation.(16) Reduced interferon responses at baseline have been linked to exacerbation risk;(17, 18) however, enhanced interferon activation during a cold is associated with increased exacerbation risk.(19) These complex relationships have been further interrogated using systems biology approaches. Altman et al. identified both common and distinct mechanisms of viral and non-viral exacerbations in urban children with exacerbation-prone eosinophilic asthma.(20) Importantly, only a minority of immune pathways associated with

asthma exacerbations in these children were impacted by systemic corticosteroid therapy, highlighting the relevance of both corticosteroid responsive and non-responsive pathways with regard to the pathogenesis of these common events.

Inhaled Corticosteroids to Prevent Exacerbations

Given their established efficacy as controller therapy in persistent asthma, many studies have examined whether the initiation or escalation of ICS therapy in the setting of loss of asthma control (ie, the “yellow zone”) would mitigate symptom progression to exacerbation. This has been studied in four general scenarios (Table 1): (1) intermittent high dose ICS without use of background controller in preschool children with recurrent episodic wheezing, (2) intermittent high dose ICS without use of background controller in adults with mild asthma, (3) as needed ICS dosing whenever rescue treatment is needed among children, adolescents, and adults with mild asthma not receiving daily controller therapy, and (4) escalation of ICS in children and adults currently receiving daily controller therapy.

Intermittent ICS Dosing

Preschool Children:

In young children who lack evidence of persistent symptoms, and thus are not prescribed daily controller therapy, the role of intermittent high dose ICS has been meta-analyzed by Kaiser *et al* and included 5 studies involving 422 participants(21). The specific ICS regimens were initiated at the first signs of URI, and varied between studies, including nebulized budesonide (1mg twice daily for 7 days), budesonide MDI (800mcg or 1600mcg twice daily for 7 days), nebulized budesonide (400mcg 4 times daily for 3 days, then 400mcg twice daily by MDI for 7 days), beclomethasone MDI (750mcg 3 times daily for 5 days), and fluticasone MDI (750mcg twice daily until symptom free for 48 hours). Overall these studies demonstrated that the initiation of high dose ICS at the early signs of symptom development in children ≤6 years with intermittent asthma or recurrent viral-triggered wheeze reduced the risk of exacerbation by 35% (95% CI 19–49%)(21). Furthermore, treatment of 6 children with this approach prevented one child from experiencing an exacerbation (NNT=6 children, 95% CI 4–12). Among children 12–53 months at increased risk for persistent asthma by virtue of a positive modified asthma predictive index, Zeiger and colleagues demonstrated no difference between daily low dose ICS (nebulized budesonide 500mcg once daily) and intermittent high dose ICS (nebulized budesonide 1mg twice daily started at onset of URI symptoms and continued for 7 days) on risk of exacerbations or asthma control(22). In sum, these data demonstrate that in preschool children with recurrent episodes of wheezing, the use of intermittent high dose ICS therapy, when applied early in the course of an emerging respiratory tract illness, is an effective strategy for the prevention of symptom progression to subsequent exacerbation requiring systemic corticosteroids. Providers should provide careful and complete verbal and written education to families about this strategy and be cognizant of the frequency of use of high dose ICS, as at least one study demonstrated adverse growth effects with intermittent use of high dose fluticasone propionate(23).

Adults with mild asthma:

Given their relatively low day-to-day symptom burden, many adults with mild asthma may choose to not use daily ICS therapy. The IMPACT randomized placebo-controlled trial compared three treatment strategies in 225 adults with mild persistent asthma: daily low dose ICS (budesonide 200 mcg twice daily), zafirlukast 20 mg twice daily, and intermittent ICS (budesonide 800 mcg for 10 days if symptoms "worsened" according to a symptom-based action plan (i.e. yellow zone))(24). Over the course of the 52-week trial, there was no significant difference in asthma exacerbations or changes in morning peak flows between the three groups. Daily ICS therapy was superior to the 2 other approaches in terms of pre-bronchodilator lung function, asthma symptom control, and markers of airway inflammation. These findings suggest that while daily ICS may provide a better overall treatment response, the use of intermittent high dose ICS, driven by a symptom-based action plan, may be an appropriate alternative strategy for adults with mild asthma.

Increased ICS in Children and Adults on Maintenance ICS

Despite limited evidence, asthma guidelines have endorsed the increased dose of ICS in children and adults prescribed a daily ICS when they begin to lose asthma control. Given the overall efficacy of ICS in the prevention of exacerbations, there has been a general approach that "more must be better". However, a Cochrane review found no evidence that doubling the dose of ICS during episodes of increased symptoms in children or adults reduced the risk of exacerbation.(25) The NHLBI AsthmaNet performed a trial to assess whether quintupling the dose of ICS during the early loss of asthma control in 5–11 year old children could reduce the risk for systemic corticosteroids.(26) In fact, this approach did not reduce the risk of asthma exacerbation, but led to a small impact on linear growth, highlighting the potential systemic effects of high doses of ICS in children. In contrast to these results, a pragmatic trial of quadrupling the dose of ICS in adults at the early signs of loss of asthma control found a 19% relative reduction in the rate of asthma exacerbations, which was associated with an increase in adverse effects of inhaled corticosteroids.(27) This begs the question, do the different findings reflect exacerbation pathogenesis in children vs. adults, differential baseline medication adherence, study design, or all of the above? Taken together, the potential for incremental benefit from this approach must be balanced with potential risks, particularly in the pediatric population.

Use of an ICS-containing controller when reliever is required – Dynamic ICS dosing

Over the past decade, increasing attention has been focused on coupling delivery of an anti-inflammatory medication whenever patients exhibit acute asthma symptoms and would otherwise use just a bronchodilatory reliever. The occurrence of asthma symptoms likely reflects uncontrolled airway inflammation, and thus titrating administration of an anti-inflammatory ICS whenever a reliever is required would serve to both alleviate acute symptoms while augmenting ICS dosing while asthma control is being lost. This concept has been convincingly demonstrated to be effective, with compelling evidence for the roles of using an ICS whenever a SABA is needed and for the use of combination inhalers with

an ICS and a rapid-onset LABA either intermittently or as part of a maintenance and reliever approach (discussed below).

Low dose ICS taken whenever SABA is taken:

In patients with mild asthma, who experience symptoms infrequently, the use of a daily controller such as low dose ICS is often not well-accepted by patients, leading to poor overall adherence. Recognizing this, four clinical trials have examined the role of administering a low dose ICS whenever patients needed SABA for relief of acute symptoms (BEST, TREXA, ASIST, BASALT). The BEST study in adults, which used a combination beclomethasone/albuterol single inhaler(28), and the TREXA study in children and adolescents, which used separate beclomethasone and albuterol inhalers(29), both demonstrated fewer exacerbations with the as needed ICS/SABA strategy compared to SABA-only therapy. In both of these studies, the groups treated with as needed ICS/SABA used less cumulative ICS. Furthermore, two clinical trials in children (TREXA and ASIST(30)) and two in adults (BEST and BASALT(31)) each showed similar or fewer exacerbations compared with maintenance ICS in patients with mild asthma. Thus, similar rates of asthma exacerbations can be achieved with less exposure to ICS. The trade-off in this approach is a greater degree of symptoms in those treated with an as-needed approach. Furthermore, there are no ICS/SABA single inhalers currently available in the US, which can make this approach less practical and challenging to implement.

As needed low dose ICS/formoterol in mild asthma:

The availability of single inhalers containing both ICS and the rapid-onset long-acting beta$_2$-agonist formoterol has allowed for study of the use of this single inhaler strategy in patients with mild asthma. Four recent trials have evaluated the efficacy of as needed low dose budesonide/formoterol in patients with adolescents and adults with mild asthma (SYGMA-1(32), SYGMA-2(33), Novel START(34), and PRACTICAL(35); summarized in Table 2). All four trials were conducted over 52 weeks. Two were conducted in a double-blind placebo-controlled fashion (SYGMA-1 and 2), while the others were open-label trials (Novel START, PRACTICAL) aimed to reflect the real-world performance of this strategy. All four trials were consistent in demonstrating the efficacy of as needed low dose ICS/formoterol, without the use of a daily controller, in reducing the risk of asthma exacerbations compared to as needed SABA. Exacerbation rates were lower using as needed ICS/formoterol compared to as needed SABA in the absence of background daily ICS (SYGMA1, Novel START) and were either superior (PRACTICAL), comparable (SYGMA1) or noninferior (SYGMA2) to twice daily maintenance ICS with SABA as rescue. Thus, in patients with mild asthma, the use of low dose ICS/formoterol as needed for asthma symptoms, without the need for any daily controller medication, is a safe and effective strategy for reducing asthma risks, and is recommended as the preferred controller/reliever approach by GINA for adolescents and adults requiring Step 1 or 2 treatment(36). Additional studies of this approach are urgently needed in children younger than 12 years of age.

Use of ICS/formoterol as Maintenance and Controller:

For patients who require daily controller therapy (GINA Steps 3–5 in children 5–11 years, adolescents, and adults),(36) the use of ICS/formoterol as both daily therapy and as a reliever has been extensively studied. Compared to the use of a SABA alone for rescue, the use of ICS/formoterol as a reliever, in conjunction with ICS/formoterol given twice daily as a controller, has been demonstrated to be superior in terms of reduction of risk of exacerbations. A recent meta-analysis examined this approach, including 16 randomized trials involving 22,748 participants(37). The authors demonstrated the use of the strategy of ICS/formoterol as both maintenance and reliever therapy (MART) in patients 12 years of age and older resulted in a significantly lower risk of exacerbations compared to the same dose of maintenance ICS/LABA with SABA used as reliever (Risk Ratio 0.68 [95% CI 0.58–0.80]) and to a higher dose of ICS/LABA with SABA used as reliever (Risk Ratio 0.77 [95% CI 0.60–0.98]). Similarly, although based on a subgroup analysis of a single trial involving 341 patients, MART therapy in patients 4–11 years of age was associated with a lower risk of exacerbations relative to a higher dose of ICS as controller therapy and SABA as rescue (Risk Ratio 0.55 [95% CI 0.32–0.94]) or the same dose of ICS/LABA as controller therapy and SABA as rescue (Risk Ratio 0.38 [95% CI 0.23–0.63]).

Conclusion

The optimal use of inhaled corticosteroids for the prevention of asthma exacerbations, balancing benefits and risks, has evolved significantly over the past decade. Suboptimal adherence to traditional treatment approaches and over-reliance of patients on SABA in the management of emerging exacerbations has driven the need to identify evidence-based approaches that patients are likely to adhere to.(38) However, significant gaps remain. While dynamic ICS dosing, particularly low-dose ICS/LABA combination therapy has shown consistent benefit in mild asthma in adolescents and adults, data in infants and children are lacking. Further, it is clear that many exacerbations are not ICS responsive and the identification of strategies to specifically target the causal inflammatory pathways at an individual level is an important unmet need to provide personalized prevention of exacerbations.

Acknowledgments

Funding:

Dr. Jackson reports funding from NIH/NIAID UM1 AI160040

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Table 1:

Yellow Zone Treatment Approaches

Baseline Therapy	Age	Approach
PRN SABA	All	Increase SABA frequency
	<5 yrs	High dose ICS
	5–11 yrs	PRN low dose ICS/SABA
	12+ yrs	PRN low dose ICS/SABA PRN low dose ICS/formoterol
Daily ICS	5–11 yrs	Continue ICS
	12+ yrs	Increase ICS 4X?
Daily ICS/formoterol	5–11 yrs	MART* (low dose ICS/formoterol)
	12+ yrs	MART* Increase ICS dose separate inhaler

* MART = maintenance and reliever therapy

Table 2:

Clinical trials of as needed ICS/formoterol in patients with mild asthma

Trial	Design	Duration	Population	Interventions	Exacerbation Outcome	Conclusion
SYGMA1	Double-blind Superiority	52 weeks	12+ yrs with mild asthma needing Step 2 treatment (N=3849)	Terb PRN BUD/FORM PRN BUD BID/Terb PRN	Annual exacerbation rates: Terb 0.20 BUD 0.09 BUD/FORM 0.07 (RR 0.36 vs Terb, 0.83 vs BUD)	Exacerbation rates were similar in BUD/FORM PRN and BUD BID groups and lower than the terbutaline PRN group
SYGMA2	Double-blind Non-inferiority	52 weeks	12+ yrs with mild asthma eligible for regular ICS (N=4215)	BUD/FORM PRN BUD BID/Terb PRN	Annual exacerbation rates: BUD/FORM 0.11 BUD 0.12 Rate ratio 0.97 (upper confidence limit 1.16)	BUD/FORM PRN was noninferior to BUD BID with respect to severe exacerbation rates
Novel START	Open label Superiority	52 weeks	18–75 yrs with mild asthma (N=668)	Albuterol PRN BUD BID/Alb PRN BUD/FORM PRN	Annualized exacerbation rates: Albuterol PRN 0.40 BUD/FORM 0.195 (RR 0.49 vs Alb) BUD BID 0.175 (RR 1.12 vs BUD/FORM)	BUD/FORM PRN was superior to albuterol used as needed in prevention of exacerbations
PRACTICAL	Open label Superiority	52 weeks	18–75 yrs with mild-moderate asthma treated with PRN SABA or low-moderate dose ICS over past 12 weeks (N=890)	BUD BID/Terb PRN BUD/FORM PRN	Annualized exacerbation rates: BUD/Form 0.119 (RR 0.69) BUD BID 0.172	BUD/FORM PRN was more effective than BUD BID/Terb PRN at preventing asthma exacerbations

Alb = albuterol; BID = twice daily; BUD = budesonide; FORM = formoterol; ICS = Inhaled corticosteroid; Terb = terbutaline; PRN = as needed; RR = rate ratio; SABA = short-acting beta-agonist