



Strategies to prevent exacerbations of childhood asthma

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Purpose of review

The goal of this review is to discuss strategies to prevent asthma exacerbations in children, focusing on recent advances in knowledge and understanding.

Recent findings

Asthma exacerbations are common, and their prevention is an important goal to avoid detrimental impacts such as loss of disease control and lung function and significant healthcare costs. A number of strategies have been studied as tools for prevention of asthma exacerbations. Daily inhaled corticosteroids (ICSs) are effective for many children with asthma. However, alternative strategies such as intermittent ICS therapy, antileukotrienes, and biologics have been studied as means to lessen corticosteroid exposure. Further, recent studies have examined add-on strategies for children not controlled with ICS alone. Finally, personalizing therapy with targeted approaches has provided significant benefit to those with moderate–severe disease.

Summary

Recent research highlights many potentially effective treatment strategies to prevent asthma exacerbations in children. We have reviewed and summarized the data on treatment approaches to help provide a better understanding of the methods that can be utilized. An individualized approach with careful monitoring is essential to identify the most effective strategies to prevent asthma exacerbations in each child.

Keywords

asthma (child), exacerbations, inhaled corticosteroids, long-acting β -agonists, personalized treatment, prevention

INTRODUCTION

Asthma exacerbations are episodes of worsening symptoms including dyspnea, chest tightness, cough, and wheezing, usually associated with a decreased lung function. Exacerbations often occur in children with severe and uncontrolled asthma but can also be problematic in those with mild disease with an overall good day-to-day symptom control [1,2]. Despite advances in medications and treatment strategies, asthma exacerbations continue to be an important problem in children [3,4]. Missed school, progressive loss of lung function, subsequent greater severity of asthma, impaired activity and sleep, along with increased healthcare costs are all potential negative impacts of asthma exacerbations [5,6].

A variety of risk factors for asthma exacerbations have been identified. Increased bronchodilator reversibility, rhinosinusitis, gastroesophageal reflux disease, and elevated blood eosinophils and IgE levels have been associated with increased exacerbation frequency both in children and adults [7]. In

children, a history of a previous exacerbation has been shown to be the strongest risk factor for future exacerbations [4].

Routine follow-up, provision of an asthma action plan, and promoting medication adherence are all important strategies to improve asthma control and prevent future exacerbations. Both the National Asthma Education and Prevention Program Expert Panel and Global Initiative for Asthma (GINA) recommend daily inhaled corticosteroids (ICS) for treatment of patients with persistent asthma to decrease airway inflammation, symptoms, and risk for exacerbations with subsequently accelerated lung function decline. In those not controlled with daily ICS,

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KEY POINTS

- Asthma exacerbations in children remain a significant problem.
- Exacerbations are associated with significant detrimental effects on hRQoL, lung function, and socioeconomics.
- Increasing the ICS dose in children in the yellow zone receiving maintenance ICS does not provide clinically relevant benefit and may lead to substantial adverse effects.
- There are multiple potential treatment strategies available to prevent exacerbations in children and an individualized approach is warranted to maximize benefit.
- Ongoing and future studies into the role of emerging biologics, vitamin D, and bacterial lysates show promise to help meet this important healthcare need in children.

the addition of a long-acting β -agonist (LABA) reduces risk of exacerbation [8,9]. Although regular use of ICS reduces exacerbation risk significantly, adherence to daily therapy is often low which can limit the effectiveness of ICS therapy. Further, for many children with asthma, exacerbations occur despite regular ICS use alone or in combination with other controller therapies such as LABA and/or leukotriene receptor antagonists (LTRA) [10]. Data are limited to guide patients, families, and clinicians in the selection of the best strategies to prevent asthma exacerbations. Therefore, this review will discuss recent evidence informing current and emerging treatment strategies to reduce the risk of asthma exacerbations in children.

Escalating inhaled corticosteroids in the 'yellow zone'

GINA recommends a temporary increase in the dose of inhaled corticosteroids at the early signs of loss of asthma control for patients who are prescribed daily inhaled corticosteroids, and this approach is commonly included in asthma treatment plans [11]. A recent Cochrane review examined the impact of increasing ICS doses to prevent exacerbations in children and adults with mild-to-moderate asthma treated with daily ICS [12[•]]. The authors concluded that there was no evidence to suggest that increased doses of inhaled corticosteroids reduced the need for rescue oral corticosteroids to treat exacerbations [12[•]]. This review primarily included studies in which the ICS dose was doubled, and there has been

suggestion that quadrupling ICS doses may be effective in adults [13].

A recent trial examined whether quintupling the dose of ICSs in children 5–11 years of age with early signs of loss of asthma control prevents exacerbations [14^{••}]. In this study, there was no difference in severe exacerbations treated with systemic corticosteroids, time to first severe exacerbation, symptom burden, albuterol use, or rate of emergency room visits, in children who temporarily increased to high-dose ICS versus continued low-dose ICS in the 'yellow zone'. Furthermore, the high-dose treatment group had higher inhaled and systemic exposure to corticosteroids as well as a small reduction in linear growth rate. In a pragmatic, unblinded study involving adolescents and adults, a 'yellow zone' quadrupling of ICS was compared with an unchanged maintenance dose [15^{••}]. Although the quadruple-dose group did have fewer severe exacerbations (45 versus 52%), the overall corticosteroid exposure was greater in the participants in the quadrupling group. Taken together, these data suggest that in children prescribed and adherent to daily ICS, temporary increases in ICS in the 'yellow zone' do not prevent exacerbations and may lead to increased corticosteroid exposure and adverse effects.

Single inhaler for maintenance and reliever therapy

The prevention of asthma exacerbations with the combined use of inhaled corticosteroids and LABA as controller and rescue therapy, termed single inhaler for maintenance and reliever therapy (SMART), is another treatment strategy that has been evaluated in children 4 years of age and above. These studies were performed in patients with asthma that was poorly controlled on ICS alone. A post-hoc analysis of six randomized, double-blind trials investigating budesonide/formoterol maintenance and reliever therapy in adolescents with persistent asthma was recently published [16[•]]. This analysis demonstrated ~50% relative reduction in exacerbation risk with SMART compared with conventional fixed-dose maintenance therapy and a SABA for relief. This reduction in exacerbations was achieved despite a lower mean daily dose of ICS. Similar findings have been observed in 4–11-year-old children [17]. Although this approach is recommended by GINA [8], it is not currently FDA approved in the United States.

Biologics and exacerbation prevention

Children who have asthma exacerbations despite treatment with medium–high doses of ICS with

or without other controller therapy represent a population with significant unmet needs. The long-term impact of exposure to high-dose ICS in children is not well studied. Personalized approaches to asthma management in this population are highly desirable, and biologic therapies show great promise in this regard.

Omalizumab, a recombinant humanized anti-immunoglobulin E monoclonal antibody, is FDA approved for use in children 6 years of age and older. Busse *et al.* demonstrated that omalizumab added to guideline-based care leads to significant reductions in asthma exacerbations in urban children and adolescents. Importantly, exacerbations were prevented despite reduced doses of ICS in the omalizumab treatment group [18]. Omalizumab was particularly effective in children sensitized and exposed to relevant allergens, highlighting the value of targeting the allergic component in this population [19]. More recently, the Preventive Omalizumab or Step-up Therapy for Severe Fall Exacerbations study demonstrated a significant reduction in exacerbations with treatment initiated prior to the return to school [20]. Children with an exacerbation during the run-in and those requiring high-dose ICS benefited most significantly from omalizumab. Further, inhibition of IgE with omalizumab was associated with reduced rhinovirus infections and virus-induced asthma exacerbations, highlighting the interaction between viruses, allergic sensitization, and type-2 inflammation in childhood asthma exacerbations [21].

Interleukin-5 (IL-5) is essential for eosinophil maturation, activation, and survival. Monoclonal antibodies directed at IL-5 (mepolizumab [22] and reslizumab [23]) or its receptor, IL-5R (benralizumab [24]), have been developed to target eosinophilic inflammation. A recent systematic review of anti-IL-5 treatments was completed, with eight of the studies including participants aged 12 years and older [25[¶]]. Data from these studies showed that anti-IL-5 medications reduced clinically significant asthma exacerbation rates by about half in participants with severe eosinophilic asthma. These agents are most effective in patients with recurrent exacerbations and high blood eosinophils. Both mepolizumab and benralizumab are currently FDA approved for ages 12 years and above; however, so far there are only limited data in this age group. Studies in school-age children and adolescents are ongoing.

Dupilumab is an anti-IL-4 receptor α monoclonal antibody that blocks IL-4 and IL-13 signaling, and therefore type 2 inflammation [26]. In a recent study, dupilumab reduced the rates of asthma exacerbations compared with placebo in patients aged 12 years and older [27[¶]]. Dupilumab was recently

FDA approved for ages 12 years and above, and studies in younger children are currently ongoing.

Alternative approaches to daily inhaled corticosteroids

Leukotriene receptor antagonists

Montelukast is a cysteinyl LTRA that is a controller therapy option for persistent asthma [8,28]. In 2–5-year-old children with persistent asthma, montelukast was shown to significantly improve symptom control compared with placebo [29]. Exacerbation rates were not statistically lower in this study, whereas the percentage of patients requiring symptomatic treatment with oral corticosteroids decreased from 28 to 19%. However, in preschool children with intermittent viral-induced asthma, montelukast reduced rates of asthma exacerbations by ~32% compared with placebo [30]. In another study, differential responses to asthma medications were assessed in children aged 12–59 months who met guideline-based criteria for daily controller therapy [31[¶]]. Among differential responders, the probability of best response was highest for daily ICS, although some patients responded best to LTRA. However, there were no predictors to identify those who were more likely to respond to LTRA versus daily ICS. The probability of best response to daily ICS was increased in those with aeroallergen sensitization and eosinophil counts greater than 300/ μ l in this particular population. In school-age children, 6–14 years of age, montelukast improved exacerbation rates compared with placebo [32]; however, ICS has been more effective in exacerbation prevention in this population [33]. Taken together, although montelukast is a potential alternative to reduce exacerbations in some children, it is not as effective as daily ICS [34].

Intermittent high-dose inhaled corticosteroid therapy

Adherence to daily ICS is often quite low [35–39], and many patients use their controller therapies in an as-needed fashion for a variety of reasons including cost, side-effects, and perceived lack of need for daily therapy. This has led to increased interest in alternative ICS administration strategies.

An initial study in adults compared high-dose intermittent ICS with low-dose daily ICS or twice daily zafirlukast [40]. Although lung function was significantly better on daily ICS, the frequency of exacerbations did not differ. A randomized trial of episodic high-dose ICS versus placebo in preschool children with recurrent wheezing showed a reduction in exacerbations treated with systemic

corticosteroids; however, this approach was associated with small reductions in growth [41]. Similarly, Zeiger *et al.* [42] investigated daily low-dose ICS compared with intermittent high-dose ICS during respiratory tract illnesses in children between 12 and 53 months of age with a history of recurrent wheezing. There was no difference in the primary outcome, the rate of exacerbations requiring oral corticosteroids between daily and intermittent ICS groups. Additionally, there were no between-group differences in symptom severity during illness or bronchodilator use. Thus, similar outcomes were achieved with lower cumulative ICS exposure in the intermittent high-dose ICS group.

There are no available studies of this approach in school-age children or adolescents. However, based upon the findings in preschool children and adults, this approach may be considered for those who prefer not to take a daily medication, or where there are concerns about steroid exposure or costs of medications. Close clinical follow-up is warranted to avoid over use of high-dose ICS and its potential adverse effects.

Symptom driven/rescue inhaled corticosteroids

Another intermittent approach to therapy involves the coadministration of an ICS and a bronchodilator (SABA or LABA) in a symptom-driven fashion. A study in 5–18-year-old children with mild persistent asthma found that while daily ICS was most effective for the prevention of asthma exacerbations, as-needed use of ICS together with a SABA reduced the risk of exacerbations compared with SABA alone [43]. There is no ICS/SABA combination product currently available in the United States, making this approach challenging to implement in clinical practice.

Formoterol is a LABA with a rapid onset of action which allows it to be used as a rescue bronchodilator. Two recent studies in adolescents and adults compared as-needed budesonide/formoterol (ICS/LABA), daily budesonide and as-needed SABA, and as-needed SABA alone. As-needed ICS/LABA and daily ICS resulted in a similar reduction in exacerbations when compared with SABA alone, despite ICS exposure of ~17% of the daily ICS treatment group [44²²]. In a similar but pragmatic study design, Bateman *et al.* [45²³] found that ICS/LABA as needed was noninferior to ICS maintenance therapy in preventing asthma exacerbations. This as-needed approach is another strategy that may be particularly useful in patients where controller adherence and cost of medications may be a significant barrier. Additionally, this method is a way to ensure delivery of anti-inflammatory corticosteroid with β_2 -agonist at the onset of early loss of asthma control.

However, the results in adolescents were not reported separately in either study and this approach has yet to be studied in children younger than 12 years of age. Furthermore, this treatment approach is not approved in all countries.

Other potential add-on therapies

Vitamin D

Low levels of 25-hydroxyvitamin D (25[OH]D) have been previously demonstrated to be associated with increased risk for asthma exacerbations in both children and adults [46,47]. A meta-analysis of seven double-blind, randomized controlled studies, five of which included children, was recently published [48²⁴]. This meta-analysis showed that vitamin D supplementation reduced the rate of asthma exacerbations requiring systemic corticosteroids compared with placebo. Subgroup analyses suggested that this effect was seen only in participants with baseline circulating 25(OH)D of less than 25 nmol/l. Thus, vitamin D may be a relatively well tolerated and inexpensive approach to help decrease the risk of severe asthma exacerbations in some children. Several randomized controlled trials are currently ongoing and aim to help clarify the potential role of vitamin D in the prevention of asthma exacerbations.

Macrolides to prevent severe lower respiratory tract infections

Bacharier *et al.* [49] examined azithromycin use early in the course of respiratory tract infections (RTIs) to prevent progression to severe lower respiratory tract infections (LRTIs) in preschool children with history of severe intermittent wheezing in the setting of LRTIs. Compared to placebo, the azithromycin group had a significantly lower risk of progression to a severe LRTI. Additionally, children receiving azithromycin had a lower symptom severity score during episodes of severe LRTI.

Although the precise mechanism of action is uncertain, azithromycin appears to be a useful strategy in preventing severe LRTIs for some children. It should be noted that this study examined the effect of azithromycin in a distinct population, preschool children who did not require controller therapy. It should also be highlighted that azithromycin was initiated early in the course of RTIs and was not used in patients already experiencing severe LRTIs.

Long-acting muscarinic antagonists

Tiotropium is a long-acting muscarinic antagonist that is FDA approved in children 6 years of age and above. It has shown ability to improve lung function and decrease asthma exacerbation risk in adults with

symptomatic asthma despite ICS or ICS/LABA therapy [50–53]. Tiotropium add-on therapy to ICS or ICS/LABA in children and adolescents with moderate and severe asthma has been shown to improve FEV1 but has not been shown to significantly reduce exacerbations [54–56]. Vrijlandt *et al.* [57] recently reported on the use of tiotropium as an add-on to ICS in children aged 1–5 years with persistent asthma. This small study reported lower rates of asthma exacerbations in those treated with tiotropium; however, additional studies are needed to examine the impact of tiotropium on exacerbations in children.

Bacterial lysates

Bacterial lysates made of a diverse array of pathogenic bacteria have been used to prevent RTIs in both adult and pediatric populations [58]. Given the link between respiratory infections and asthma exacerbations, recent studies have examined the potential role of bacterial lysates in wheezing and exacerbation prevention. OM-85 BV (Broncho-Vaxom) is a lysate obtained through alkaline proteolysis of eight different bacterial pathogens of the upper respiratory tract. This product has shown ability to reduce the frequency and duration of wheezing episodes in children [59]. A recent study examined the use of polyvalent mechanical bacterial lysate (PMBL) in the prevention of exacerbations in children 6–16 years of age with persistent allergic asthma [60]. Although there was no difference in the primary outcome (Asthma Control Test scores) between the treatment and placebo groups, the authors found a significantly lower mean number of asthma exacerbations in the PMBL group. Further investigation into this treatment strategy to reduce respiratory illnesses and associated exacerbations is warranted.

Allergen immunotherapy

Allergen immunotherapy (AIT) is another potential add-on therapy for those with underlying allergic sensitization and symptoms on exposure. Subcutaneous immunotherapy has been associated with decreased asthma symptoms and medications in children with allergic asthma, but studies have yet to show a significant reduction in exacerbations [61,62]. Virchow *et al.* [63] examined adults with persistent asthma and allergic rhinitis with sensitization to house dust mite (HDM) and found that sublingual immunotherapy (SLIT) for HDM was associated with a decrease in mild-to-moderate asthma exacerbations. Although GINA endorses SLIT for adults with allergic rhinitis, sensitization to HDM, and asthma not adequately controlled on ICS [11], further adequately powered studies are

needed to assess the role of AIT in preventing asthma exacerbations in children.

CONCLUSION

Acute exacerbations continue to be a significant burden in childhood asthma. The detrimental impacts of exacerbations include hRQoL, accelerated loss of lung function, worsening severity of asthma, missed school, and increased healthcare costs. Although there is still relatively limited evidence to guide treatment approaches, emerging data have helped further elucidate several potentially beneficial strategies to prevent asthma exacerbations in children. The common practice of escalation of ICS in the ‘yellow zone’ in patients taking daily ICS does not appear to provide a clinically relevant exacerbation protection in children and may be associated with significant risks of adverse effects. Current and emerging biologic therapies are highly effective in preventing exacerbations in patients with moderate–severe disease and provide the ability to personalize therapy in this population. Further studies to lessen the acute and chronic consequences of asthma exacerbations are essential to reduce the burden of asthma across all ages.

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Conflicts of interest

D.J.J. reports grants from NHLBI, NIAID, and GlaxoSmithKline. He has received consulting fees from Boehringer Ingelheim, Commense, GlaxoSmithKline, and Vectura and served on a data monitoring committee for Pfizer.

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