

Prevention and Outpatient Treatment of Asthma Exacerbations in Children



Clare S. Murray, MBChB, MD^a, Daniel J. Jackson, MD^b, and W. Gerald Teague, MD^c *Manchester, UK; Madison, Wis; and Charlottesville, Va*

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

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Learning objectives:

1. To differentiate the phenotypic characteristics and symptom patterns of children with severe treatment refractory asthma from those children at risk for momentary lapses in symptom control.
2. To learn to use rigorous monitoring methods including symptoms, exposure to trigger factors, and past exacerbation patterns so as to effectively intervene with appropriate pharmacotherapies to prevent or limit exacerbations.
3. To identify ineffective treatment responses to short-acting bronchodilators and controllers in the ambulatory settings in a timely way to direct children for acute care and reduce morbidity from wheeze exacerbations.

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Acute exacerbations cause significant morbidity and mortality in children with asthma worldwide. Although exacerbations can be minor and transient, in some children they are recurrent and significantly adversely impact quality of life. Children with frequent exacerbations account for a disproportionate amount of unscheduled care in nonprimary health facilities. Frequent exacerbators are often prescribed controller medications, but poor adherence is common. Major predictors for asthma

exacerbations include genetic, social, comorbid, biological, and environmental factors. Although virus infections are a key trigger for exacerbations, other environmental factors also significantly increase risk. A previous exacerbation is a major risk factor for future exacerbations and thus identifies children to target for prevention of future episodes. In this review, we discuss both modifiable and fixed factors associated with asthma exacerbations, how to assess children for risk, and which

^aDivision of Infection, Immunity, and Respiratory Medicine, School of Biological Sciences, University of Manchester, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

^bDivision of Allergy, Immunology and Rheumatology, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wis

^cDivision of Respiratory Medicine, Allergy, Immunology, and Sleep, and The Child Health Research Center, Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, Va

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Corresponding author: Clare S. Murray, MBChB, MD, Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Education and Research Centre (2nd Floor), Manchester University NHS Foundation Trust, Southmoor Road, Manchester M23 9LT, UK. E-mail: Clare.murray@manchester.ac.uk. 2213-2198

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Abbreviations used

ALOX5- Arachidonate 5-lipoxygenase

DBRCT- Double-blind randomized controlled trial

ED- Emergency department

GINA- Global Initiative for Asthma

ICS- Inhaled corticosteroid

LABA- Long-acting β -agonist

LTRA- Leukotriene receptor antagonist

OCS- Oral steroid

SABA- Short-acting β_2 -agonist

pharmacological and nonpharmacological interventions may be of benefit. Finally, we review the current evidence around treatment within the outpatient setting for an emerging exacerbation. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:2567-76)

Key words: Asthma; Child; Exacerbation

Asthma is the most prevalent chronic respiratory disease worldwide.¹ In the year 2016 alone, more than 339 million people had asthma and accounted for 417,918 deaths.² In 2013, the estimated cost of asthma in the United States alone was almost \$82 billion.³ Asthma is more prevalent in children than adults. In the United States, as recently as the year 2007, 1.7 million emergency department (ED) visits (0.64 million children) and 456,000 hospital admissions (157,000 children) were attributed to asthma exacerbations.⁴ It has been estimated that patients with exacerbations have approximately double the health care costs.⁵ The CDC MMWR reported a small reduction in asthma attacks in children in the United States between 2001 and 2016, but more than half of asthmatic children had at least 1 asthma attack in 2016.⁶ ED visits occurred in 16.7% of children with asthma in 2016, but this differed significantly by race and ethnicity: white, non-Hispanic 12.2%, black non-Hispanic 22.5%, and Hispanic 16.2%.⁷ Similarly, the most recent data from asthma hospitalizations from 2013 demonstrate a disproportionate burden in black (6.8%) and Hispanic (5.8%) versus white (3.3%) children.⁸

Poor symptom control is common in asthma despite the advent of new and often highly effective controller therapies.⁹ However, access to these treatments is relatively limited in special populations including children due to underinsurance, pharmacy plan restrictions, and relatively high costs.¹⁰ The result has been a steady change in the locus of acute asthma care in children from the primary care setting to utilization of expensive ambulance services and treatment in the emergency room setting.¹¹ Children with asthma enrolled in both private and government-sponsored insurance plans have significantly greater all-cause pharmacy and medical costs compared with children without asthma.

FEATURES OF CHILDREN WITH RECURRENT ACUTE HEALTH CARE UTILIZATION FOR ASTHMA

Children with recurrent utilization of acute care facilities to treat asthma exacerbations have unique phenotypic characteristics.¹² A recent meta-analysis identified multiple risk factors for repeated ED visits and hospitalizations due to asthma.¹³ However, the authors noted a limited number of quality studies on

this important health care issue. Key questions remain: (1) why are these children at heightened risk; (2) what specific exposures contribute to these events; and (3) how can we modify risk and improve therapy in a targeted fashion for each child?

Children with recurrent episodes of troublesome wheeze despite treatment with low-to medium-dose inhaled corticosteroids (ICS) are often referred to as having “problematic or difficult wheeze.” They do not necessarily have severe asthma, insofar as once remediable factors are addressed, a substantial proportion can demonstrate good symptom control.¹⁴ For example, in 311 children referred to an academic medical center with repeated episodes of cough and/or wheeze, only 126 (40%) were found to have severe asthma after detailed diagnostic evaluation.¹⁵ Approximately two-thirds had been admitted to the hospital with refractory symptoms, including nearly one-third to the intensive care unit.

Scope and definition of exacerbations

Children with asthma often can have symptoms that are effectively relieved by short-acting bronchodilators. Such episodes, even though self-limited, may be frequent and impair exercise performance, sleep, and school performance. The prevalence of symptoms widely varies, but in a “real-world” study, the majority of patients (55%) reported uncontrolled asthma despite common treatment with combination ICS/long-acting β -agonist (LABA) controllers.⁹

A mild-to-moderate episode of poor symptom control is one limited to 48 hours of symptoms and does not progress in response to rescue medication use.¹⁶ By contrast, significant exacerbations are those with troublesome symptoms that last for at least 48 hours and ultimately result in treatment with a systemic corticosteroid. Severe exacerbations that cannot be relieved with acute care in an ED and require hospital admission are termed “status asthmaticus” and can be life-threatening.

Patient-centric impact

Exacerbations are a rare cause of mortality in children.¹⁷ More often, asthma exacerbations disrupt the child’s and care givers’ quality of life. For example, exacerbations interfere with school attendance and participation in sports, and result in parental loss of work and income due to the necessity of providing acute care to the involved child.¹⁸ Nocturnal symptoms are an important cause of sleep disruption in children with asthma, resulting in inattentiveness at school, parental stress, and fatigue. Repeated cough episodes, a robust symptom of an evolving exacerbation, interfere with the affected child’s attention span and often disrupt the classroom and may even result in a child’s temporary exclusion from school.

RISK FACTORS FOR EXACERBATIONS

Risk factors for frequent asthma exacerbations in children encompass genetic, social, comorbid, biological, and environmental domains (Figure 1).

Genetic factors

Genetic studies confirm that candidate genes for asthma risk are related to but often unique from those associated with exacerbations and disease progression.¹⁹ CDHR3 is a gene associated with exacerbations that functions as the receptor for rhinovirus C.²⁰ Genes related to gene-environment interactions (CDHR3, TGFB1, IL9, CHIT1, CHI3L1, CD14, ADAM 33),

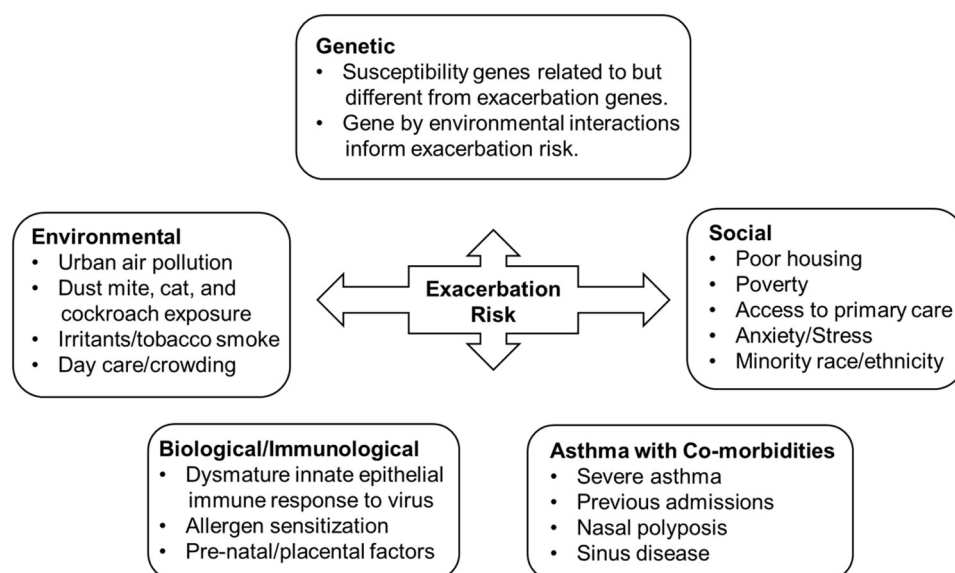


FIGURE 1. Schematic illustrating confluence of interdependent risk factors promoting asthma exacerbations in children.

asthma pathogenesis (CRTAM, IL4Ra, IL13, ORMDL3, CTNNA3, SEMA3D), pharmacogenetics (IL4Ra, ADRB2, LTC4S, LTA4H, ST13), and treatment response (FCER2, CRTM1, P2RX7) inform exacerbation risk through a broad spectrum of biological pathways.²¹⁻²⁵ Genetic factors interact with race, medication exposure, environmental exposures, and innate/adaptive immune responses to triggers such as pollution, viruses, and allergens to determine exacerbation risk. Recent work in the Inner City Asthma Consortium leveraged systems immunology to identify coordinated airway immune responses that differentiate a cold that progresses to exacerbation from one that resolves without significant asthma flare.²⁶ Further studies are needed to leverage these observations toward novel effective therapies.

Social factors

Sociocultural factors strongly inform asthma symptom control and exacerbation risk. Relevant social determinants of health include economic stability, education and health care access, neighborhood housing conditions, and community/social interactions.²⁷ Public health and hospital admissions data show that minorities residing in urban environments have disparately greater death rates and overall asthma mortality compared with their counterparts in census tracts with higher income status and housing standards. However, in studies adjusting for community and family socioeconomic variables and environmental exposure variables, ED use for asthma care was similar in black and white patients, and the primary factor attributed to increased ED use in blacks was lack of access to preventive primary care.²⁸ Effective interventions directed at adverse social determinants of health in patients with asthma include education programs at neighborhood churches,²⁹ community coalitions and health fairs, and novel social media platforms. Within the health system, intensive education programs and utilization of asthma coaches are effective ways to improve asthma outcomes.³⁰

The Boston Children's Hospital Community Asthma Initiative is a case management plan using education and coordination

to address racial inequality.³¹ This program significantly reduced asthma admissions from targeted communities.

Disease-related and comorbid factors

Patients at significant risk for a future exacerbation include those who have required an ED visit or admission for status asthmaticus in the past.³² Likewise, asthma severity is an important determinant. In one study, approximately one half of patients with severe asthma had 3 or more exacerbations in the previous year, compared with 5% to 13% of patients with mild-moderate asthma.³³ Obesity is another risk factor for asthma exacerbations in children that crosses genetic, social, and biological domains. Obesity conferred minor increased risk of exacerbations and no clear link to symptom control in a recent meta-analysis report.³⁴ Prevalent comorbidities associated with poor symptom control in the Severe Asthma Research Program include sinus disease, and in adolescents, nasal polyposis.³⁵

Biological factors

In a Costa Rican ED study, children with atopic sensitization to dust mite had a greater probability of wheeze in response to rhinovirus infections compared with children without sensitization.³⁶ A UK study demonstrated a significant synergistic effect between sensitization and exposure to aeroallergens and viral infection (especially rhinovirus) resulting in almost a 20-fold increase in hospital admission with asthma exacerbation.³⁷ Experimental rhinovirus inoculation studies demonstrate significant augmentation of blood eosinophilia and prolonged symptoms in atopic compared with nonatopic asthmatics.³⁸ Furthermore, longitudinal studies have identified a differential impact of risk factors by season in urban children.³⁹ In addition, similar to adults, elevated serum IL6 levels, a marker of systemic inflammation, have been identified as a risk factor for exacerbation in urban children, regardless of T2 biomarker status.⁴⁰ Unlike adults however, IL6 was not associated with asthma severity, control, or loss of lung function in children.

Environmental factors

Exposure to outdoor air pollution is an important trigger for asthma exacerbations in urban environments. In metropolitan Atlanta, the level of ambient ozone and other primary pollutants exceeds safety standards and is associated with an increase in acute ED visits for wheeze.⁴¹ During the 1996 Atlanta Olympic Games, a reduction in ground ozone concentrations associated with traffic mitigation efforts results in a significant (42%) fall in asthma-related events across a broad metropolitan area.⁴² Children with asthma who reside adjacent to urban traffic corridors on the US Mexico border had greater expired nitric oxide and reduced lung volumes, an effect not found in their healthy counterparts.⁴³

Indoor exposures significantly contribute to asthma exacerbation risk. The Institute of Medicine issued in 2000 a summary report based on a critical review of available evidence that exposure to allergens produced by house dust mites, cats, and cockroaches is causal as triggers that aggravate symptoms in sensitized children with established asthma.⁴⁴ In preschool children, symptoms are worsened by contact with secondhand tobacco smoke. Furthermore, the Institute reported that mitigation of these factors can improve symptom control. Studies going as far back as 1993 support the adverse effects of passive tobacco smoke and exacerbations of asthma in children.⁴⁵ More recent studies support vaping as an important cause of life-threatening status asthmaticus in teenagers.⁴⁶

There is likewise strong evidence to support a causal role of indoor dampness and mold exposure as triggers for asthma exacerbations in children.⁴⁷ In the long-term Childhood Asthma Management Program study, exposure to indoor endotoxin, a part of the outer cell wall of gram-negative bacteria, reduced exacerbation risk, whereas mold exposure imposed greater risk.⁴⁸ Mouse allergens are commonly found in US houses and schoolrooms,⁴⁹ and exposure to mouse allergen in schools was associated with increased asthma symptoms and reduced lung function.⁵⁰ There is a striking diversity of prevalent allergens in regional environments based on weather and the ambient humidity. In warm climates with higher indoor humidity, cockroach and dust mite are prevalent allergens, whereas in colder regions, mouse allergen appears to predominate. Even within climate zones there can be differential exposures to domestic allergens, such as urban cockroach exposure versus dust mite in affluent suburbs.⁵¹

Among indoor irritants, schoolroom exposure to acrolein, a ubiquitous aldehyde found in both indoor and outdoor air, was found to be a greater stimulus for asthma exacerbations compared with formaldehyde in a large cohort of children.⁵² Challenges in the voracity of reviews evaluating links between indoor air quality exposures and asthma exacerbations are the limitations of meta-analyses *per se*, and in previous studies, failure to include acrolein as a criterion irritant.

PHARMACOLOGICAL INTERVENTIONS TO PREVENT EXACERBATIONS

This section will focus on long-term management to prevent asthma exacerbations. Strategies to interrupt emerging exacerbations will be discussed below.

Standard therapy

ICS are the preferred therapy for the treatment of persistent asthma across the ages (Expert Panel Report 3 and Global

Initiative for Asthma [GINA] 2019^{53,54}). Studies in preschool and school-age children have demonstrated that ICS are most effective in improving asthma control and exacerbation prevention in children with evidence of type 2 inflammation.^{55,56} Montelukast has also been used as an alternative to ICS. Data have been mixed with regard to montelukast and exacerbation prevention in preschool children.^{57,58} In school-age children, montelukast has been shown to improve exacerbation rates compared with placebo; however, ICS has been more effective in exacerbation prevention.^{56,59} Although montelukast is a potential option to reduce exacerbations in some children, it is typically not as effective as daily ICS.

In patients not controlled with daily ICS, the addition of a LABA often reduces risk of exacerbation.⁶⁰ The addition of a long-acting muscarinic antagonist modestly reduces exacerbation risk in adults,⁶¹ but studies to date in children have yet to demonstrate significant benefit in this domain of asthma control. Furthermore, 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).⁶²

Biologics and exacerbation prevention

Children who have asthma exacerbations despite treatment with medium-high doses of ICS $\pm$ other controller therapies have significant unmet health care needs. Precision approaches to asthma management in this population are needed, and biologic therapies have demonstrated significant advances for this high-risk population.

Omalizumab, anti-IgE antibody, added to guideline-based care leads to significant reductions in asthma exacerbations in urban children and adolescents. Notably, exacerbations were prevented despite reduced doses of ICS in those treated with omalizumab.⁶³ Omalizumab provided significant benefit in children sensitized and exposed to relevant allergens, demonstrating the importance of the allergic component of disease in these children. Subsequently, the Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) study demonstrated a significant reduction in exacerbations with treatment initiated before the high-risk fall season.⁶⁴ Blockade 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.⁶⁵ Monoclonal antibodies directed at IL5 (mepolizumab^{66,67} and reslizumab⁶⁸) or its receptor, IL5R (benralizumab⁶⁹), have been developed to target eosinophilic inflammation. These studies suggest that anti-IL5 medications reduce asthma exacerbation rates by approximately 50% in participants with severe eosinophilic asthma. Anti-IL5 agents are most effective in patients with frequent exacerbations and elevated blood eosinophils. Data to date in pediatric populations have been limited,⁷⁰ but studies in school-age children and adolescents are ongoing.⁷¹ Dupilumab is an anti-interleukin-4 receptor α monoclonal antibody that blocks IL4 and IL13 signaling to broadly interfere with type 2 inflammation.⁷² In adolescents and adults, dupilumab has been shown to significantly reduce the rates of asthma exacerbations compared with placebo.⁷³ Results of a recent study of dupilumab in 6- to 11-year-olds have not yet been reported. In addition, dupilumab has shown significant benefits in atopic dermatitis and therefore

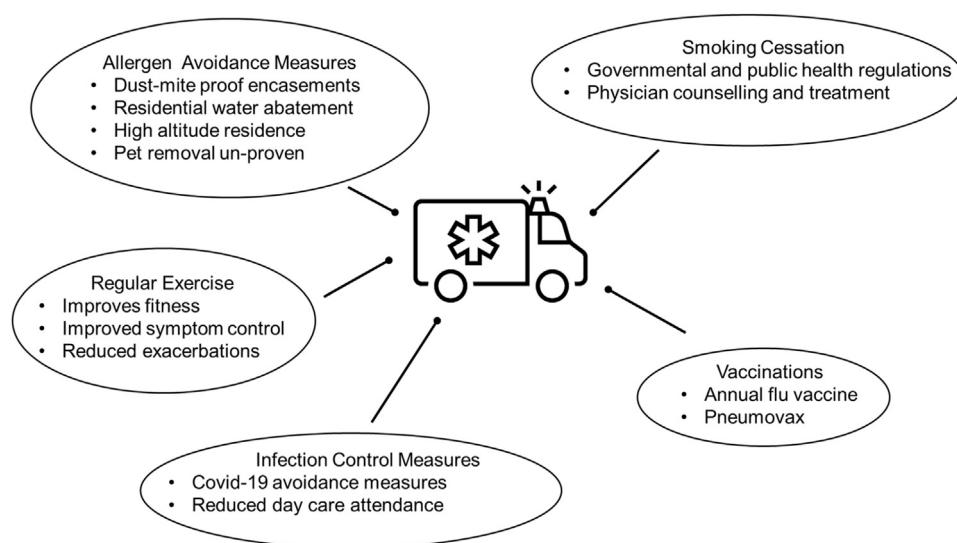


FIGURE 2. Practical nonpharmacological interventions to prevent or limit asthma exacerbations in children.

may be especially helpful in the subgroup of children with very severe eczema and severe asthma.⁷⁴

NONPHARMACOLOGICAL INTERVENTIONS TO PREVENT EXACERBATIONS

A number of non-pharmacological interventions have been suggested to prevent or limit asthma exacerbations in children (Figure 2).

Allergen avoidance measures

Although published Cochrane reviews on both house dust mite⁷⁵ and pet allergen avoidance⁷⁶ have concluded that avoidance measures are not useful in the treatment of asthma, these strategies may still be of use. There is little doubt that moving to a mite-free environment, such as high altitude, has resulted in significant benefits to sensitized asthmatic children.⁷⁷ However, this strategy is certainly not practical for the majority. Most would recommend the removal of soft furnishings and carpets, damp dusting, acaricides, mite impermeable bed covers, or a combination of some or all of the above.⁷⁸ Most methods will diminish the amount of allergen exposure, but their effect on asthma control remains debatable. However, a recent double-blind randomized controlled trial (DBRCT) of mite-impermeable bedding in dust mite-sensitized asthmatic children demonstrated a 45% reduction in emergency hospital attendance with asthma exacerbation.⁷⁹

Whether to advise the removal of pets in sensitized asthmatics is also a matter of controversy, with little to no evidence available.⁸⁰ Various methods to reduce pet allergen in homes with pets have been tried in the research setting, such as washing pets and air filtration units, but none of these have demonstrated any consistent clinical benefits.⁸¹⁻⁸³

Children sensitized and exposed to molds have been shown to have increased symptoms and unscheduled visits,^{84,85} and controlled trials aimed at reduction of water infiltration, removal of water-damaged building materials, and improvement of heating and ventilation have shown significant improvements in symptoms and exacerbation rates.⁸⁶

Current guidelines recommend multicomponent interventions targeting the inhalant allergen to which the individual is sensitized or having symptoms with; it is recognized that a single intervention often is inadequate.⁸⁷

Smoking cessation

A systematic review of 25 pediatric studies of asthma and second-hand smoke demonstrated that children exposed to second-hand smoke were more than twice as likely to be hospitalized for asthma and had significantly more ED or urgent care visits than those who were not exposed.⁸⁸ In a real-world study in Scotland, UK, after a national ban of smoking in public places in 2006, childhood asthma admissions fell significantly in all age groups. A subsequent public health initiative in 2014 aimed to reduce domestic exposure of children to second-hand smoke, “Take it right outside,” led to a significant decrease in asthma admissions among children aged under 5 years relative to the underlying trend, but not in older children.⁸⁹ Smoking cessation advice and reduction of smoke exposure in asthmatic children should continue to be part of all pediatric asthma consultations.

Vaccinations and infections

A recent systematic review and meta-analysis demonstrated that influenza vaccine prevented between 59% and 78% of asthma attacks leading to hospitalization and/or ED visits; therefore, annual vaccination against influenza should be recommended in all asthmatics.⁹⁰ In young children with exacerbation-prone asthma, it has been suggested that targeted pneumococcal conjugate booster vaccination in those with low antibody responses to pneumococcal vaccine serotypes can significantly reduce asthma exacerbations requiring corticosteroids.⁹¹

During the recent COVID-19 pandemic, data suggest that pediatric emergency admissions and attendance at ED with asthma reduced significantly compared with previous years’ activity, suggesting the importance of person-to-person transmission of viruses in the pathogenesis of asthma exacerbations.⁹² Of course, the importance of pollution reduction and alteration in exposure to aeroallergens may also be playing a significant role

TABLE I. Treatment of emerging exacerbation in the outpatient setting

Treatment	School-age children	Preschool children
β_2 -Agonists	Give via pMDI and spacer	Give via pMDI and spacer
Anticholinergics	No evidence for use	No evidence for use
Oral corticosteroids	Give short course prednisone or dexamethasone	May be of benefit in those with asthma phenotype
Inhaled corticosteroids*		
Not on regular ICS	7-10 days' treatment at the start of usual viral trigger	7-10 days' treatment at the start of usual viral trigger
On regular ICS	Not recommended	Not recommended
Antibiotics	Not recommended†	Azithromycin 12mg/kg/day for 5 days at the start of usual viral trigger
LTRA	Not recommended	Not recommended

ICS, Inhaled corticosteroid; LTRA, leukotriene receptor antagonist; pMDI, metered dose inhaler.

*In place of oral corticosteroids.

†Unless concomitant bacterial infection suspected.

during these “lock-down” situations. It is reassuring that data emerging from the COVID-19 pandemic suggest that people with asthma have a similar risk to or even lower risk than those without asthma for acquiring COVID-19 and have similar clinical outcomes.⁹³ The underlying reasons for this remain unclear.

Outdoor exercise mitigation in urban environments

Exercise in patients with asthma is complex, as physical activity often provokes asthma symptoms, and thus patients often avoid exercise and take on a sedentary lifestyle. In adult asthmatics, accumulating evidence suggests that regular exercise not only improves physical fitness but has also been shown to improve overall control and reduce exacerbations.⁹⁴

Vitamin D supplementation

Several observation studies have linked vitamin D deficiency with asthma exacerbations, perhaps explained by immunomodulatory and anti-inflammatory effects of vitamin D. However, a meta-analysis of clinical trials showed that vitamin D3 supplementation was associated with lower risk of asthma exacerbations, but this was not significant in children.⁹⁵ A recent DBRCT of vitamin D3 supplementation in high-risk children with asthma aged 6 to 16 years taking low-dose ICS and with low serum 25-hydroxyvitamin D levels (<30 ng/mL) did not significantly improve the time to a severe exacerbation.⁹⁶ Although it remains good practice to screen and treat those at risk of vitamin D deficiency, evidence to date does not suggest that this will improve asthma exacerbation rates.

TREATMENT OF EXACERBATIONS IN THE OUTPATIENT SETTING

Despite optimal maintenance treatment and avoidance of risk factors, asthma exacerbations will still occur, particularly in exacerbation-prone children. In the outpatient setting, early recognition of an exacerbation and treatment may prevent significant deterioration and hospitalization. There are, however, a limited number of interventions (Table I).

β -Agonists

Short-acting β_2 -agonists (SABA, eg, levalbuterol, albuterol, salbutamol) are the mainstay of reliever treatment. In the outpatient setting, these are usually given by a metered-dose inhaler and large-volume spacer device, as children are less likely to have tachycardia and hypoxia than when the same drug is given via a nebulizer.⁹⁷ Relatively large doses can be given in

rapid sequence over a short space of time, giving almost immediate relief of symptoms with few side effects.

Anticholinergics

Ipratropium bromide is an anticholinergic agent that produces bronchodilation probably by inhibiting cholinergic bronchomotor tone. Adding ipratropium bromide to an inhaled SABA in severe exacerbations decreases rates of hospitalizations and shortens ED stays for children with severe or moderate-to-severe asthma exacerbations.⁹⁸ However, the benefit of ipratropium bromide to SABA therapy is seen primarily in more severe asthma exacerbations, and there is no evidence for its use in the outpatient setting where SABA with a spacer device is sufficient to control symptoms. It may be useful in patients who find side effects of SABA such as palpitations or tremor troublesome.

Corticosteroids

The early use of oral steroids (OCS) in EDs can reduce the need for hospital admission and prevent a relapse in symptoms after initial presentation.⁹⁹ The benefits from OCS can be apparent within 3 to 4 hours, and thus in the outpatient setting with an emerging exacerbation, early dosing with OCS can prevent further deterioration and the need for the ED. Traditionally, prednisone has been the OCS of choice, usually being prescribed for 3 or 5 days in children. However, more recently dexamethasone has been suggested as an alternative being given in a single-dose or 2-dose regime. Currently, head-to-head comparisons are limited, and there is insufficient evidence to suggest that dexamethasone offers an advantage over prednisone for the management of mild-to-moderate acute asthma in children.^{100,101}

The advice to use high-dose or increased dose ICS in an emerging exacerbation remains somewhat controversial. GINA currently recommends that for those patients taking ICS maintenance treatment, the dose should be increased when there is a clinically important change in the patients' usual asthma control.⁵⁴ However, a recent Cochrane review concluded that there was no evidence indicating that doubling the dose of inhaled glucocorticoids in response to increasing symptoms decreased asthma exacerbations in children or adults.¹⁰² A recent DBRCT in children aged 5 to 11 years of quintupling ICS dose for 7 days at the first sign of loss of asthma control showed no reduction in those exacerbations requiring OCS rescue.¹⁰³ However, it should be noted that patients using maintenance and reliever budesonide and formoterol

combination have been shown to have fewer exacerbations than those on standard therapy with SABA reliever,¹⁰⁴ including children aged 4 to 11 years, albeit with limited evidence.¹⁰⁵ It can be postulated that the benefit of this regime over increased dose of standard ICS maybe due to the very early intervention that this schedule permits. In addition, it is recognized that the effects of such studies can be significantly influenced by the underlying adherence rate, and real-world studies may give more accurate results.⁸⁷ An additional study of this approach in young children is needed.

Antibiotics

Antibiotics are not recommended for use in an asthma exacerbation unless an underlying bacterial infection is strongly suspected (fever, purulent sputum, very wet cough in a young child).⁵⁴ However, there is some evidence to suggest that macrolide antibiotics and the ketolide antibiotic, telithromycin, may have a beneficial effect on asthma exacerbations through their antibacterial and/or anti-inflammatory properties. Although a DBRCT in adults using telithromycin¹⁰⁶ and an open-labeled study in children using clarithromycin¹⁰⁷ have shown some benefit over standard exacerbation treatment, current real-world evidence suggests that macrolide use has no significant benefit in acute asthma compared with other common antibiotics such as amoxicillin,¹⁰⁸ and a recent Cochrane review concluded that there was insufficient evidence on the topic.¹⁰⁹ A further recent large real-world study found that although antibiotics were frequently prescribed in relation to asthma exacerbations, contrary to guideline recommendations, the addition of antibiotics to OCS in the management of asthma exacerbations conferred little clinical benefit.¹¹⁰ Considering the risks of antibiotic overuse and microbial resistance, their use in asthma exacerbation should be confined to treatment of significant concurrent bacterial infection.

Considerations in the preschooler

It is clear that preschool children presenting with acute wheeze are a mixed group of phenotypes, and it is often difficult to determine whether a preschool child with wheeze actually has asthma. In those without a diagnosis of asthma who present with preschool wheeze, it is still advisable to give OCS, but caution needs to be taken in those with frequent episodes. It must be noted that in a large UK study of children presenting with an attack of wheezing associated with a viral infection, a 5-day course of oral prednisolone was not superior to placebo in reducing the duration of hospitalization or other secondary outcomes, even amongst those deemed to be at high risk of having asthma.¹¹¹

In preschool children, with viral-induced wheeze, preemptive high-dose ICS may reduce exacerbation rate compared with placebo,¹¹² but evidence does not support doubling or increasing ICS dose at the first indication of an emerging exacerbation in children taking daily ICS.¹¹³ Recently published guidelines suggested differing approaches dependent on whether adherence was assumed or not. For those with recurrent wheezing triggered by respiratory tract infections and not taking regular ICS, the recommendation is starting a short course of daily ICS at the onset of a respiratory tract infection along with as-needed SABA.⁸⁷

Preemptive use of azithromycin has also been trialed in this age group with some promising results. The APRIL trial was a DBRCT of azithromycin in 1- to 6-year-olds with significant

episodic wheeze; participants were randomized to start treatment early in an upper respiratory tract illness thought likely to proceed to an exacerbation, and resulted in azithromycin reducing the risk of exacerbation by 36%.¹¹⁴ Another study in 1- to 3-year-olds with recurrent asthma-like symptoms, randomized children with symptoms for at least 3 days, to azithromycin or placebo for 3 days and demonstrated a significant reduction in the duration of symptoms in the active group, with the effect size increased in those treated early.¹¹⁵ However, too few episodes requiring OCS or admission to hospital occurred for this secondary outcome to be assessed.

The use of LTRA has also been proposed as a therapy for exacerbations of wheeze in preschool children. A few studies have investigated the use of intermittent montelukast to prevent OCS use for exacerbation, but there is little evidence of significant clinical benefit.¹¹⁶ One study, however, highlighted the importance of the arachidonate 5-lipoxygenase (ALOX5) gene promoter, which has been shown to modify montelukast response in adults.¹¹⁷ Children in the 5/5 ALOX5 promoter stratum had significant reductions in unscheduled medical attendances for wheeze, compared with those in the placebo group.

GAPS IN KNOWLEDGE

Asthma exacerbations result from complex interactions among host factors, environmental exposures, and subsequent activation of airway inflammatory pathways. Therapies to target type 2 inflammatory pathways have the potential to significantly reduce exacerbation risk; however, therapies to target patients with T2-low asthma remain a major unmet need. Although evidence supports early intervention with azithromycin at the onset of a cold, as means to reduce symptom progression in preschool children with recurrent wheeze,¹¹⁴ it is not known whether azithromycin is effective in acute wheeze episodes in children and adolescents with colds who are on maintenance ICS. Multiomics approaches are needed to unravel the complex interactions that lead to the development of asthma exacerbations. This work may additionally inform disease prevention strategies in early life.

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