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Invited Review Article

Severe asthma in children: Evaluation and management

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ABSTRACT

Severe asthma in children is associated with significant morbidity. Children with severe asthma are at increased risk for adverse outcomes including medication-related side effects, life-threatening exacerbations, and impaired quality of life. It is important to differentiate between severe therapy resistant asthma and difficult-to-treat asthma due to comorbidities. The most common problems that need to be excluded before a diagnosis of severe asthma can be made are poor medication adherence, poor medication technique or incorrect diagnosis of asthma. Difficult to treat asthma is a much more common reason for persistent symptoms and exacerbations and can be managed if comorbidities are clearly addressed. Children with persistent symptoms and exacerbations despite correct inhaler technique and good medical adherence to standard Step 4 asthma therapies according to the guidelines^{1,2}, should be referred to an asthma specialist with expertise in severe asthma.

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Introduction

Asthma is a chronic respiratory disease that affects people of all ages and is characterized by episodic and reversible attacks of wheezing, chest tightness, shortness of breath, and coughing.³ According to Centers for Disease Control and Prevention (CDC) 2016 report, prevalence of asthma in children aged 5–11 years and 12–17 years is 9.6% and 10.5% respectively. Overall prevalence of asthma in children under 18 years old in US is reported as 8.3%.⁴ According to Severe Asthma Research Program (SARP) III cohort, children with asthma, regardless of asthma severity, were male, with normal lung function and normal body mass index. Compared to adults, children with severe asthma have significantly higher number of eosinophils, allergen sensitizations and higher IgE levels.⁵ Majority of children with asthma respond well to standard therapies, however a significant proportion still have severe disease that is resistant to conventional therapies. According to International Study of Asthma and Allergies in Childhood (ISAAC), global prevalence of severe asthma among adolescents is 6.9%, ranging from 3.8% in Asia-Pacific and Northern and Eastern Europe to 11.3%

in North America.⁶ Severe asthma is an important health burden as children with severe asthma are prone to medication related side effects, life threatening exacerbations, and impaired quality of life.⁷ Progressive air flow limitation is also a feature of severe asthma.⁸ Most importantly, poor asthma control leads to poor quality of life in children and caregivers.^{9–11}

Definition of severe asthma

According to the ATS/ERS guideline,² severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroid) to prevent it from becoming “uncontrolled” or remains “uncontrolled” despite this therapy.¹² Most children with asthma achieve symptom control with low to medium doses of inhaled corticosteroids (ICS); however, there is a small but significant group of children with severe asthma who require higher dose of ICS with an additional controller medication to maintain symptom control or they remain uncontrolled despite this therapy.¹ A birth cohort followed children over 10 years for development of asthma. Among those children who were diagnosed with asthma, 4.5% had “severe asthma” and overall prevalence of severe asthma within that birth cohort was 0.5%.¹³

It is important to differentiate between severe asthma and difficult to treat asthma. Difficult to treat asthma is a much more common presentation for persistent symptoms and exacerbation. By definition, difficult to treat asthma is associated with poor

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control due to an incorrect diagnosis or associated comorbidities, poor medication adherence, psychological or environmental factors.¹⁴ This can be controlled if comorbidities are clearly addressed. In contrast, treatment resistant asthma is defined as difficult asthma despite addressing and managing these factors.

The most common problems that need to be excluded before a diagnosis of severe asthma can be made are poor medication adherence, poor medication technique, incorrect diagnosis of asthma with symptoms due to upper airway dysfunction, cardiac failure or poor fitness. The child should be evaluated for possible comorbid diseases such as rhinosinusitis, gastroesophageal reflux, obesity or obstructive sleep apnea (Table 1).² In addition to these, environmental allergen control is an important contributor to poor asthma control. Ongoing allergen or irritant exposure at home or school will end up with difficult to treat asthma.¹⁵

Asthma causes high psychiatric morbidity. Psychosocial assessment of the child and the caregiver is important. Children with severe asthma has significant anxiety and difficulty in coping with their disease,^{16,17} which can lead to poor medication adherence and asthma control. In addition, caregiver's psychosocial stress is associated with high asthma morbidity regardless of medication adherence. Depressive symptoms in the caregiver are important and associated with beliefs and attitudes that may significantly influence asthma management and adherence to asthma medications,¹⁸ which might again lead to poor asthma control.

Evaluating a child with severe asthma

Clinicians should have a high degree of suspicion regarding the diagnosis of asthma and evaluate the patient if the symptoms present asthma. Misdiagnosis of non-asthmatic conditions as uncontrolled asthma has been reported to be as high as 12–30%.^{12,19,20} Many other conditions can mimic asthma (asthma masqueraders) such as vocal cord dysfunction, anatomic abnormalities e.g. tracheobronchomalacia, and other obstructive lung diseases such as cystic fibrosis or bronchiolitis obliterans (Table 2).^{2,15} Addressing comorbidities, poor adherence to asthma controller medications, inadequate medication technique, and psychological and environmental factors are important next steps for a definitive diagnosis.²¹

Confirmation of diagnosis

The initial step to confirm the diagnosis consists of a detailed history including the outline of respiratory symptoms, triggers for cough, wheeze, shortness of breath, and chest tightness, previously trialed treatments and response to those treatments, and a detailed family history questioning any respiratory problem.²¹ After doing a detailed physical examination, the next step is obtaining a spirometry with pre and post bronchodilator responses. Short-acting inhaled bronchodilators should not be used within 4 hours of testing. Long-acting beta agonist bronchodilators (LABA) (e.g. salmeterol or formoterol) and oral therapy with aminophylline or slow-release beta agonists should be stopped for 12 hours prior to the test.²² It is essential to assess inspiratory flow–volume curves to rule out fixed or dynamic central airway obstruction. It is

Table 2

Differential diagnosis of severe asthma in children.

Dysfunctional breathing
Vocal cord dysfunction (VCD)
Panic attacks
Swallow dysfunction and chronic silent/micro aspiration
Anatomic abnormalities/External compression
Congenital vascular malformations (e.g. vascular ring)
Tracheobronchomalacia
Mediastinal mass
Enlarged lymph node
Tracheoesophageal fistula
Cystic Fibrosis
Primary ciliary dyskinesia
Protracted bacterial bronchitis
Congenital or acquired immune deficiency
Bronchiectasis
Bronchiolitis obliterans
Interstitial Lung Diseases
Connective Tissue Diseases
Vasculitis
Congenital heart diseases
Foreign body aspiration
Bronchopulmonary Dysplasia
Endobronchial mass/tumor
Hypersensitivity Pneumonitis

important to remember that children with severe asthma will have normal lung function or might show mild airflow obstruction at baseline, if not presenting with an acute exacerbation. Increased distal resistance with small airway involvement, with no large airway involvement, likely explains the often normal FEV₁ values. Other spirometric parameters such as FEV₁/Forced vital capacity (FVC), FEF_{25–75%} predicted, or the post bronchodilator response in FEV₁ may be more reflective of asthma severity.^{2,23–25} Post-bronchodilator response of 12% and 200 mL increase in FEV₁ compared with baseline FEV₁ suggest a “significant” bronchodilator response²⁶; however 8% increase in FEV₁ after bronchodilator may be more sensitive to evaluate response in children.²⁷ If there is no evidence of obstruction on spirometry, then bronchoprovocation testing with methacholine or exercise challenge needs to be performed.² A chest radiograph is also necessary to rule out anatomic abnormalities of airways, lung parenchyma and heart.

Additional work up to rule out alternative diagnoses should be guided by clinical suspicion or atypical presentation. Developmental failure, poor weight gain, wet productive cough, stridor, rapidly declining lung function, absence of atopy should raise suspicion for other diagnosis.² In those cases, high resolution computed tomography, bronchoscopy with bronchoalveolar lavage (BAL), sweat chloride testing, nasal or airway ciliary biopsy, basic immune workup including quantitative immunoglobulin levels with antibody responses, pH/impedance probe or video fluoroscopic swallow study needs to be considered to rule out bronchiectasis, parenchymal or airway disorders, cystic fibrosis, primary ciliary dyskinesia, immunodeficiency, gastroesophageal reflux and aspiration disorders respectively.^{2,15,21} Bronchoscopy and BAL will help to rule out protracted bacterial bronchitis. In addition, BAL will help to differentiate between the different phenotypes of airway inflammation described in children with severe asthma; eosinophilic inflammation, paucigranulocytic inflammation and neutrophilic inflammation.¹⁴

After confirming the diagnosis of asthma, next step is to differentiate between difficult-to-treat asthma which is poorly controlled due to comorbidities, poor medication adherence, and environmental exposures; and severe asthma which remains uncontrolled despite assessment and control of these factors. It is shown that after systematic evaluation of children referred as severe asthma, 30–50% of them are eventually diagnosed as difficult-to-treat asthma.^{2,28}

Table 1
Comorbidities affecting asthma control.

Rhinosinusitis
Obesity
Gastroesophageal reflux disease
Vocal cord dysfunction
Obstructive sleep apnea
Psychological disorders
Medication (ACE inhibitors, β blockers, Aspirin and other NSAIDs)

Factors affecting asthma control

Childhood asthma is associated with comorbidities that leads to poor asthma control. Addressing them is very important for better asthma control.⁷ SARP III cohort in children showed that increased BMI, GERD, sinusitis are significantly associated with exacerbation frequency.²⁹ Evaluation for those disorders should be considered.

After confirmation of asthma diagnosis and addressing these comorbidities, the next step is assessment of medication compliance, the technique of medication delivery, psychological and environmental factors. Poor adherence is common, and associates with poor asthma control.³⁰ Objective assessment is important. It is always challenging that patient self-reports are rarely consistent with objective assessment of medication adherence.^{31,32} At least 80% medication adherence to inhaled corticosteroids is shown to be optimal to keep asthma symptoms under control.³³ Pharmacy record reviews, dose counters, canister weights, and electronic monitoring devices are examples of objective assessment of medication compliance. Canister weight and doser measurements were shown to be the most reliable methods to assess medication adherence.³² It is also important to remember that adherence rates tend to decrease over time, clinician must assess medication adherence during each clinical visit. Communication and discussions of treatment efficiency between care giver, patient, physician and health care team is important to improve medication adherence. Collaboration with the school nurse is also very valuable to improve asthma management, especially if the adherence is the major contributor for poor asthma control.³⁴ Direct observational administration of morning dose of inhaled corticosteroid in school setting has been shown to improve asthma control and better quality of family life, and decrease asthma related school absenteeism, functional limitation, night time asthma symptoms as well as use of rescue medications.^{35,36} Inadequate medication administration technique is also a major contributor to poor asthma control. A study assessing children ages 8 through 16 with asthma showed that only 8.1% of children completed metered dose inhaler steps correctly.³⁷ Reviewing the medication delivery steps, demonstrating to the patient and asking patient to repeat these steps during every clinical visit are important to ensure that patient is receiving the medication appropriately.

Home environment assessment is also important for asthma management. Previous studies showed that more than 80% of school-aged children with asthma are sensitized to at least one indoor allergen.³⁸ Almost all children with severe asthma were shown to have allergen sensitivity.³⁹ Home environmental assessment provides an opportunity to assess ongoing allergen exposure such as dust mite, molds, pets, mice, cockroaches, second hand smoke or other pollutants.⁴⁰ Previous studies on indoor allergen exposure focused only on home environment and found an association between environmental exposures in the inner-city home environment and childhood asthma morbidity. It is important to remember that children spend at least 6–8 hours per day in school. Given this, school can be accepted as an occupational setting for children. Recent studies showed that school environment is a significant source of allergen exposure.^{41–43} Classroom-specific airborne endotoxin levels are shown to be significantly associated with increased symptoms scores in children with asthma.⁴¹ Clinical assessment is required especially if symptoms worsen during school year or get better during school vacation days.^{15,42}

Management

Several asthma cohorts have been recruited over the years to understand the heterogeneity in severe asthma.^{29,44–46} Classification approaches have led to the identification of severe asthma

phenotypes associated with different clinical characteristics, pathophysiology, and pathobiologic mechanisms. These different phenotypes may explain the heterogeneous responses to usual asthma medications observed in severe asthma and guide newer add-on therapies.⁴⁷

The National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP) has described clinical severe asthma phenotypes in both adults and children that can be evaluated in the clinical setting.^{23,29,45} Cluster analysis in SARP defined 4 phenotypic asthma groups in children that differed primarily according to asthma duration, the number of asthma controller medications and lung function.²³ Children in cluster 1 had relatively normal lung function and less atopy. Children in cluster 2 had slightly lower lung function, more atopy, and increased symptoms and medication use. Cluster 3 had greater comorbidity, increased bronchial responsiveness, and lower lung function. Cluster 4 had the lowest lung function and the greatest symptoms and medication use.²³ Although Clusters 3 and 4 did not completely conform to definitions of asthma severity proposed by current treatment guidelines, they were associated with differential and limited response to asthma therapies.⁴⁸ That to be said, children in Cluster 4 had best response with fluticasone/salmeterol but children in cluster 3 had poor response to guideline-based asthma treatment.⁴⁸ Studies in adults and children have shown that clinical phenotypes give an idea about asthma heterogeneity, but they are not precise enough to guide targeted immunomodulatory therapy without a biological marker to define underlying pathogenic heterogeneity and predict response to therapy.^{45,49–51}

There are two major different endotypes defined for asthma: Type 2 (T2)-high asthma and T2-low asthma, based on the type of underlying airway immune-mediated inflammation.⁵⁰ T2-high asthma is typically characterized by eosinophilic inflammation, triggered by cytokines such as interleukin-25 (IL-25), IL-33, and thymic stromal lymphopoietin, and then sustained by IL-4, IL-5, and IL-13 from cells of both the innate and adaptive immune systems, including T helper 2 (Th2) cells, invariant T cells, natural killer cells, eosinophil/basophil progenitor cells, and type 2 innate lymphoid cells.⁵⁰ This eosinophilic endotype is the most common in childhood; it clinically matches with the early-onset severe asthma, characterized by uncontrolled symptoms, more atopy, impaired lung function, increased AHR, increased number of exacerbations, and steroid responsiveness compared with the other phenotypes.^{11,50} For example; SARP III cohort showed that children with high blood eosinophil counts and FeNO levels showed better clinical response to systemic triamcinolone therapy.⁵² In contrast, T2-low asthma presents with neutrophilic or, less commonly, paucigranulocytic inflammation, sustained by IL-8, IL-17A, IL-2, and other T cell-related cytokines, as well as epithelial cell-derived cytokines.^{53–55} T2-low asthma endotype is rarely seen in children, presents with severe asthma, shows corticosteroid insensitivity.^{50,54,56}

Biomarkers associated with clinical phenotypes

BAL with bronchoscopy and bronchial biopsy are the gold standard to assess airway inflammation and remodeling in asthma; however, non-invasive techniques are more ideal, especially in children, given the necessity of safe and repeatable measurements to monitor treatment efficacy and disease progression.^{50,57} Induced sputum technique is also considered to assess airway inflammation,⁵⁸ however the complexity of the techniques limits its use in younger children. The most established biomarkers in asthma are related to eosinophilic inflammation and/or type 2 immune response.⁵⁹ The common biomarkers used in clinical practice are blood or sputum eosinophils, serum IgE, serum periostin, and fractional exhaled nitric oxide (FeNO).⁵⁰

Serum eosinophilia does not always correlate with airway eosinophilia in children with severe asthma. However, it is shown that it has the highest correlation with sputum eosinophilia when compared with other markers such as FeNO or periostin.^{60,61} Several studies have shown that serum eosinophil count correlates well with severity of asthma in children and steroid responsiveness.^{50,52,62,63} Children with higher blood eosinophil counts experience more asthma attacks than those with lower eosinophil counts.⁶⁴ Blood eosinophil count is also accepted as a marker to follow on omalizumab therapy response in children with severe asthma.⁶⁵ When available, sputum analysis for eosinophils can provide evidence for type of airway inflammation and cytokines involved in disease process. Sputum eosinophilia is shown to correlate with airway hyperreactivity and inversely associates with FEV1 in children.⁵⁰ Monitoring sputum eosinophilia also helps to monitor corticosteroid response.^{66,67} A Cochrane review showed that guiding asthma therapies based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations.⁶⁸

Nitric oxide has been defined in the pathophysiology of lung diseases, including asthma. NO acts as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator.⁶⁹ The measurement of exhaled NO has been standardized for clinical use especially in school aged children.⁷⁰ FeNO correlates with eosinophilic inflammation and is recommended in the diagnosis of eosinophilic airway inflammation. FeNO is recommended to identify children with allergic asthma who are likely to respond to ICS treatment and follow up on response to ICS therapy.^{70–74} A Cochrane review showed that modifying asthma medications based on FeNO levels compared to guideline-based management significantly decreased the number exacerbations but did not affect daily inhaled corticosteroid doses. The use of FeNO to guide asthma therapy in children may be beneficial in a subset of children, however it cannot be recommended for all children with asthma.^{50,70,75}

Elevated total serum immunoglobulin E (Ig E) and allergen specific Ig E levels are consistent with T2-high asthma. A birth cohort from New Zealand showed that asthma was strongly related to serum IgE levels. They found that none of the children with IgE levels less than 32 IU/mL had asthma, whereas 36% of those with IgE levels of at least 1000 IU/mL had asthma. In addition, the cohort showed significant correlation of IgE levels with bronchial hyper-responsiveness to methacholine challenge.⁷⁶ Omalizumab is the first biological therapy approved for severe asthma. Omalizumab binds to IgE molecule, preventing free IgE from interacting with IgE receptors on mast cells, basophils and other immunologic cells, and prevents allergic inflammation. Children above 6 years of age with total serum IgE level above 30 units/mL are candidate for anti IgE therapy. Total IgE levels should be checked to assess for Omalizumab therapy as well.

Periostin is a novel biomarker, secreted by airway epithelial cells and lung fibroblasts following induction by IL-4 and IL-13.⁷⁷ It is shown to be involved in many pathogenic processes in asthma, such as airway remodeling, subepithelial fibrosis, eosinophil recruitment, and regulation of mucus production from goblet cells. Studies in children showed that periostin levels are correlated with AHR.⁷⁸ However in children, other disease processes such as atopic dermatitis or chronic rhinosinusitis can also lead to high periostin levels, making it difficult to use as a diagnostic marker of severe asthma in children.⁵⁰

Treatment

Children with persistent symptoms and frequent exacerbations despite appropriate inhaler technique and good adherence to standard Step 4 asthma treatments should be referred to an asthma specialist with expertise in management of severe asthma.^{1,2,79} A

step-up therapy is recommended if the symptoms are confirmed to be due to asthma, inhaler technique and adherence are satisfactory, and modifiable risk factors such as allergen or smoke exposure have been addressed.² According to Global Initiative on Asthma (GINA) 2018 guideline,¹ add-on treatments that might be considered at Step 5 therapy are listed in Table 3.

Long acting muscarinic antagonists

Tiotropium, a long-acting anticholinergic bronchodilator, has been indicated for the treatment of chronic obstructive pulmonary disease for more than 10 years. GINA guidelines include tiotropium delivered by mist inhaler as an add-on therapy option at Steps 4 and 5 in patients aged above 12 years with uncontrolled asthma despite treatment with ICS and LABA.^{80,81} Tiotropium is the only long acting muscarinic antagonist (LAMA) approved for asthma in USA (patients ≥ 6 yo), Japan (patients ≥ 15 yo), and in Singapore and the European Union (patients ≥ 18 yo). In adults with poorly controlled asthma despite the use of ICSs and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided improvement in FEV₁.⁸⁰ In a study on adolescents, it is shown that tiotropium add-on therapy improved lung function in patients with moderate asthma, showing statistically significant improvement in FEV₁ at week 24 of therapy.^{81,82}

Oral corticosteroids

Although systemic corticosteroid therapy is listed as a treatment option for severe asthma management, there is no protocol to guide this therapy in children. A short-term course of systemic corticosteroids can be used to achieve asthma control. The lowest effective dose should be used, and the dose should be gradually decreased to the lowest dose that can maintain asthma control. Meanwhile, other non-steroid medications such as biological therapies or long acting anticholinergic drugs need to be considered for severe asthma management. Frequent use of systemic steroids increases the risks for adverse events including adrenal suppression, obesity, high blood pressures, bone fractures and osteoporosis.^{15,83–85}

Biologic therapies

Biologic therapies are increasingly being considered in patient with severe asthma. Biologic therapies currently in market are targeting T2-high asthma, which is characterized by significant effect of Ig E, IL-4, IL-5 and IL-13. Omalizumab, a monoclonal antibody (mAb) against immunoglobulin E (anti-IgE), was the first biologic developed for the treatment of severe allergic asthma. Mepolizumab, Reslizumab, Benralizumab and Dupilumab are the new biologic drugs approved and currently used in patients with severe asthma (Table 4).^{86,87}

Table 3
Management of severe asthma.

Optimization of ICS/LABA dose
Oral corticosteroids
Long acting muscarinic antagonist
Tiotropium
Sputum guided treatments
Phenotype-guided add-on therapies
Anti IgE therapy
Anti-IL5 therapy
Anti-IL5 receptor therapy
Anti- IL4/IL13 therapy
Nonpharmacological therapies
Bronchial Thermoplasty

Table 4

Biologic drugs currently approved for children with severe asthma.

Drug Biologic effect Brand Name	Target Population	Mode of Administration & Dosing	Clinical Effects	Adverse Effects
Omalizumab Anti-IgE mAb Xolair	≥6yr	SC every 2–4 weeks	↓ Asthma exacerbations, ↓ symptoms, ↑ FEV1 ↑ QOL, ↓ ICS dose, ↓ hospitalization, ↓ seasonal exacerbation	Anaphylaxis (<0.2%) Headache Pharyngitis Injection site reactions
Mepolizumab Anti-IL5 mAb Nucala	≥12yr	SC every 4 weeks	↓ Asthma exacerbations, ↓ symptoms, ↑ FEV1 ↑ QOL, ↓ ICS dose	Headache Pharyngitis Hypersensitivity reactions
Reslizumab Anti-IL5 mAb Cinqair	≥18yr	IV every 4 weeks	↓ Asthma exacerbations, ↓ symptoms, ↑ FEV1 ↑ QOL, ↓ ICS dose	↑ CPK (20%), Myalgia (1%) Pharyngitis Anaphylaxis (<1%)
Benralizumab Anti-IL5 mAb Fasenra	≥12 yr	SC every 4 or 8 weeks	↓ Asthma exacerbations, ↓ symptoms, ↑ FEV1 ↑ QOL, ↓ ICS dose	Hypersensitivity reactions Headache, Pharyngitis Injection site reactions
Dupilumab Anti-IL4 receptor α mAb (blocks IL-4 & IL-13) Dupixent	≥12 yr	SC once weekly	↓ Asthma exacerbations, ↑ FEV1	Anaphylaxis Hypersensitivity reactions Pharyngitis

CPK, Creatinine Phosphokinase; FEV₁, Forced expiratory flow in 1 second; IgE, Immunoglobulin E; ICS, inhaled corticosteroid; IL, interleukin; IV, intravenous; mAb, monoclonal antibody; SC, subcutaneous; QOL, quality of life; yr, years old.

Anti-immunoglobulin E

Omalizumab is a subcutaneous injectable recombinant humanized IgG1 monoclonal anti-IgE antibody that is administered every 2–4 weeks to patients with chronic allergic asthma and with sensitization to at least one aeroallergen and an elevated serum IgE level (>30 units/mL). Omalizumab decreases levels of circulating free IgEs by binding to the constant region of the IgE molecule, preventing free IgE from interacting with IgE receptors on mast cells, basophils and other immunologic cells.⁸⁸ The dose and dosing frequency are determined according to the total serum IgE level and bodyweight before initiating therapy. Studies in children with severe asthma showed significant effects of Omalizumab on reducing the rate of severe exacerbations and hospitalizations, with improvement in asthma control and quality of life in affected children. The studies also showed significant improvement in lung function as well as less steroid requirement after 1 year of Omalizumab therapy.^{89,90} A Cochrane review also showed that Omalizumab was significantly effective in reducing the dose of inhaled steroids.⁹¹ The PROSE (Preventative Omalizumab or Step-up Therapy for Fall Exacerbations) study by Teach *et al.* found that omalizumab use initiated 4–6 weeks before return to school reduced fall asthma exacerbations, particularly in those children with severe asthma requiring step 5 treatment as defined by guidelines.^{79,92,93}

Anti-IL-5 medications

IL-5 is a pro-eosinophilic cytokine that recruits eosinophils from the bone marrow, endorses the activation and endurance of these cells, resulting in eosinophilic inflammation in the airways. There are 3 anti-IL-5 biologic therapies that have been trialed in adolescent and adult asthma; mepolizumab, reslizumab, and benralizumab. None of these biologic therapies have been trialed in children under the age of 12 years. Mepolizumab and reslizumab are

humanized monoclonal antibodies against IL-5. Benralizumab is a humanized monoclonal antibody against the IL-5 receptor.⁸⁷

Mepolizumab

Mepolizumab is a humanized monoclonal antibody, which directly binds to IL-5. By binding circulating IL-5, mepolizumab prevents binding of IL-5 to IL-5R on eosinophils and prevents its action.⁹⁴ Mepolizumab was shown to reduce asthma exacerbations by approximately half in participants with severe eosinophilic asthma, improve quality of life, and result in better asthma control in patients treated with high-dose inhaled oral glucocorticoids.⁹⁵ Studies also showed statistically significant increase in pre-bronchodilator FEV₁ with mepolizumab therapy. There was no serious adverse event with mepolizumab, indeed a reduction in serious adverse events were noted in favor of mepolizumab that could be due to a beneficial effect on asthma-related serious adverse events.^{95–98} Mepolizumab is also shown to improve health related quality of life in patients with severe eosinophilic asthma.⁹⁸ Mepolizumab is approved for patients above 12 years of age, with an absolute eosinophil count ≥150 cells/μL at presentation or ≥300 cells/μL within 12 months before initiation. The dose for asthma is 100 mg administered subcutaneously every 4 weeks.⁹⁹

Reslizumab

Reslizumab is another humanized monoclonal antibody against IL-5, blocking binding of IL-5 to IL-5R, like Mepolizumab. Currently it is approved for patients with severe asthma who are at least 18 years old and with eosinophil count ≥400 cells/μL.⁹⁴ The recommended dosage regimen is 3 mg/kg once every 4 weeks administered by intravenous infusion.¹⁰⁰ Studies on Reslizumab included patients aged 12–75 years old, with eosinophilic asthma and showed less clinically significant asthma exacerbations, improved FEV₁, improved health related quality of life compared to placebo. There was no significant difference in the number of serious adverse events occurring compared to placebo.^{97,101,102}

Benralizumab

Benralizumab is a humanized, anti-eosinophilic monoclonal antibody against IL-5 receptor alpha, which is expressed on the surface of eosinophils and basophils. Two RDBPCTs (phase 3) showed that benralizumab significantly improved exacerbation rates and asthma symptoms in adolescents and adults aged 12–75 years with severe uncontrolled asthma on high-dose ICS and LABA therapy.^{103,104} Health related quality of life was also significantly improved in patients treated with benralizumab.^{97,103} The commonly reported adverse effects were worsening asthma, upper respiratory tract infections, and nasopharyngitis.^{103,104} The recommended dose is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks by subcutaneous injection.^{94,105}

Anti-IL-4/IL-13 therapy

Dupilumab

Dupilumab is a humanized monoclonal antibody against IL-4 receptor α , blocks the receptor which is shared by both IL-4 and IL-13 and critical in signal transduction. A RDBPCT study including patients aged 12 years old or older with uncontrolled moderate to severe asthma showed that Dupilumab reduced the number of severe asthma exacerbations, increased FEV₁ resulting in overall better asthma control ($P < 0.001$).¹⁰⁶ Another study on adults with glucocorticoid dependent severe asthma showed that Dupilumab treatment significantly reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV₁ ($P < 0.001$).¹⁰⁷ Dupilumab is recently approved by FDA as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. The recommended dose is 400–600 mg as initial dose, followed by 200–300 mg given every other week.¹⁰⁸

Novel biologics under investigation

CRTh2 is a prostaglandin D₂ (PGD₂) receptor, expressed on adaptive and innate immune cells. Binding of PGD₂ to CRTh2 receptor mediates chemotaxis of ILC2s and Th2 cells, leading to the release of the type 2 cytokines IL-4, IL-5, and IL-13. Fevipiprant is a CRTh2 antagonist. Phase 3 studies of Fevipiprant showed improved FEV₁, improved asthma control and decrease in sputum eosinophil count, especially in patients with high T2- High asthma.^{109,110} Thymic stromal Lymphopoietin (TSLP) is an airway derived cytokine responsible from airway inflammation. TSLP acts on dendritic cells, mast cells, ILC-2 cells, and eosinophils. TSLP triggers secretion of IL-4, IL-5, and IL-13 from Th2 cells. Tezepelumab is a novel anti-TSLP monoclonal antibody. In a phase 3 trial, tezepelumab decreased the exacerbation frequency and increased the pre-bronchodilator FEV₁ significantly in adult population.¹¹¹ Current evidence on these biological therapies is only on adult population, completed studies did not include children.

Bronchial thermoplasty

Bronchial thermoplasty is a bronchoscopic therapy delivering radiofrequency energy to the airways. Bronchial thermoplasty reduces airway smooth muscle mass and smooth muscle hypertrophy. The US Food and Drug Association approved bronchial thermoplasty for the treatment of adults with severe asthma, with uncontrolled symptoms despite treatment with inhaled corticosteroids and long-acting bronchodilators. The prognosis of bronchial thermoplasty on patients with severe asthma is not clear. It improves the quality of life, reduces the missed school/work days,

however it causes higher risk of hospitalization and adverse events as wells as higher costs. Current literature is only on adults. It is not recommended as a treatment option for children.^{1,2}

Conclusion

Pediatric severe asthma represents a clinical challenge and requires a multidisciplinary approach. The management requires careful evaluation to confirm the diagnosis, rule out asthma masqueraders, address and treat the comorbid diseases, optimize medication compliance and address environmental and psychosocial factors that affect asthma control. After careful diagnosis, optimizing medication adherence and addressing comorbid diseases, management requires individualized and targeted therapies such as long acting muscarinic antagonists and biological therapies. Defining pediatric asthma phenotypes clearly and eventually precise phenotype-targeted therapies will hopefully improve asthma outcomes in future.

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Conflict of interest

The authors have no conflict of interest to declare.

References

- Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. 2018. Available from: <http://www.ginasthma.org>. [Accessed 11 October 2018].
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;**43**:343–73.
- Kliegman R, Stanton B, St. Geme JW, Schor NF, Behrman RE. *Nelson textbook of pediatrics (Edition 20.)*. Philadelphia, PA: Elsevier; 2016.
- Zahrn HS, Bailey CM, Damon SA, Garbe PL, Breyse PN. Vital signs: asthma in children – United States, 2001–2016. *MMWR Morb Mortal Wkly Rep* 2018;**67**:149–55.
- Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline features of the severe asthma Research program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract* 2018;**6**:545–54. e4.
- Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;**64**:476–83.
- Fleming L, Wilson N, Bush A. Difficult to control asthma in children. *Curr Opin Allergy Clin Immunol* 2007;**7**:190–5.
- Fitzpatrick AM, Teague WG. Progressive airflow limitation is a feature of children with severe asthma. *J Allergy Clin Immunol* 2011;**127**:282–4.
- Bellin MH, Osteen P, Kub J, Bollinger ME, Tsoukleris M, Chaikind L, et al. Stress and quality of life in urban caregivers of children with poorly controlled asthma: a longitudinal analysis. *J Pediatr Health Care* 2015;**29**:536–46.
- Hossny E, Caraballo L, Casale T, El-Gamal Y, Rosenwasser L. Severe asthma and quality of life. *World Allergy Organ J* 2017;**10**:28.
- Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, et al. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. *Eur Respir J* 2015;**46**:1322–33.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;**43**:343–73. *Eur Respir J* 2018;**52**. <https://doi.org/10.1183/13993003.52020-2013>.
- Lang A, Carlsen KH, Haaland G, Devulapalli CS, Munthe-Kaas M, Mowinkel P, et al. Severe asthma in childhood: assessed in 10 year olds in a birth cohort study. *Allergy* 2008;**63**:1054–60.
- Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. *J Allergy Clin Immunol Pract* 2014;**2**:489–500.
- Barsky EE, Giancola LM, Baxi SN, Gaffin JM. A practical approach to severe asthma in children. *Ann Am Thorac Soc* 2018;**15**:399–408.
- Gillaspie SR, Hoff AL, Mullins LL, Van Pelt JC, Chaney JM. Psychological distress in high-risk youth with asthma. *J Pediatr Psychol* 2002;**27**:363–71.
- Lavoie KL, Bouthillier D, Bacon SL, Lemiere C, Martin J, Hamid Q, et al. Psychologic distress and maladaptive coping styles in patients with severe vs moderate asthma. *Chest* 2010;**137**:1324–31.

18. Bartlett SJ, Krishnan JA, Riekert KA, Butz AM, Malveaux FJ, Rand CS. Maternal depressive symptoms and adherence to therapy in inner-city children with asthma. *Pediatrics* 2004;**113**:229–37.
19. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003;**22**:478–83.
20. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, et al. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;**179**:1121–31.
21. Ramratnam SK, Bacharier LB, Guilbert TW. Severe asthma in children. *J Allergy Clin Immunol Pract* 2017;**5**:889–98.
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–38.
23. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of health/National heart, lung, and blood Institute severe asthma Research program. *J Allergy Clin Immunol* 2011;**127**:382–9. e1–13.
24. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske Jr RF, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;**170**:426–32.
25. Kanchongkittiphon W, Gaffin JM, Kopel L, Petty CR, Bollinger ME, Miller RL, et al. Association of FEF25%-75% and bronchodilator reversibility with asthma control and asthma morbidity in inner-city children with asthma. *Ann Allergy Asthma Immunol* 2016;**117**:97–9.
26. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;**26**:948–68.
27. Tse SM, Gold DR, Sordillo JE, Hoffman EB, Gillman MW, Rifas-Shiman SL, et al. Diagnostic accuracy of the bronchodilator response in children. *J Allergy Clin Immunol* 2013;**132**:554–9. e5.
28. Bracken M, Fleming L, Hall P, Van Stiphout N, Bossley C, Biggart E, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child* 2009;**94**:780–4.
29. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med* 2017;**195**:302–13.
30. Chan AH, Stewart AW, Foster JM, Mitchell EA, Camargo Jr CA, Harrison J. Factors associated with medication adherence in school-aged children with asthma. *ERJ Open Res* 2016;**2**.
31. Krishnan JA, Bender BG, Wamboldt FS, Szeffler SJ, Adkinson Jr NF, Zeiger RS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. *J Allergy Clin Immunol* 2012;**129**:112–8.
32. Jentzsch NS, Camargos PA, Colosimo EA, Bousquet J. Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. *Allergy* 2009;**64**:1458–62.
33. Lasmar L, Camargos P, Champs NS, Fonseca MT, Fontes MJ, Ibiapina C, et al. Adherence rate to inhaled corticosteroids and their impact on asthma control. *Allergy* 2009;**64**:784–9.
34. Lemanske Jr RF, Kakumanu S, Shanovich K, Antos N, Cloutier MM, Mazyck D, et al. Creation and implementation of SAMPRO: a school-based asthma management program. *J Allergy Clin Immunol* 2016;**138**:711–23.
35. Harrington CB, Langhans E, Shelef DQ, Savitz M, Whitmore C, Teach SJ. A pilot randomized trial of school-based administration of inhaled corticosteroids for at-risk children with asthma. *J Asthma* 2018;**55**:145–51.
36. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst Rev* 2017;**4**:Cd012226.
37. Sleath B, Ayala GX, Gillette C, Williams D, Davis S, Tudor G, et al. Provider demonstration and assessment of child device technique during pediatric asthma visits. *Pediatrics* 2011;**127**:642–8.
38. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;**323**:502–7.
39. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG. Features of severe asthma in school-age children: atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol* 2006;**118**:1218–25.
40. Gold DR, Adamkiewicz G, Arshad SH, Celedon JC, Chapman MD, Chew GL, et al. NIAID, NIEHS, NHLBI, and MCAN Workshop Report: the indoor environment and childhood asthma-implications for home environmental intervention in asthma prevention and management. *J Allergy Clin Immunol* 2017;**140**:933–49.
41. Lai PS, Sheehan WJ, Gaffin JM, Petty CR, Coull BA, Gold DR, et al. School endotoxin exposure and asthma morbidity in inner-city children. *Chest* 2015;**148**:1251–8.
42. Ety B, Phipatanakul W. School exposure and asthma. *Ann Allergy Asthma Immunol* 2018;**120**:482–7.
43. Sheehan WJ, Permaul P, Petty CR, Coull BA, Baxi SN, Gaffin JM, et al. Association between allergen exposure in inner-city schools and asthma morbidity among students. *JAMA Pediatr* 2017;**171**:31–8.
44. Moore WC, Bleeker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National heart, lung, and blood Institute's severe asthma Research program. *J Allergy Clin Immunol* 2007;**119**:405–13.
45. Fitzpatrick AM, Moore WC. Severe Asthma Phenotypes – how should they guide evaluation and treatment? *J Allergy Clin Immunol Pract* 2017;**5**:901–8.
46. Gibson PG, Henry RL, Thomas P. Noninvasive assessment of airway inflammation in children: induced sputum, exhaled nitric oxide, and breath condensate. *Eur Respir J* 2000;**16**:1008–15.
47. Opina MT, Moore WC. Phenotype-Driven therapeutics in severe asthma. *Curr Allergy Asthma Rep* 2017;**17**:10.
48. Chang TS, Lemanske Jr RF, Mauger DT, Fitzpatrick AM, Sorkness CA, Szeffler SJ, et al. Childhood asthma clusters and response to therapy in clinical trials. *J Allergy Clin Immunol* 2014;**133**:363–9.
49. Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, et al. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. *J Allergy Clin Immunol* 2010;**125**:1028–36. e13.
50. Licari A, Castagnoli R, Brambilla I, Marseglia A, Tosca MA, Marseglia GL, et al. Asthma endotyping and biomarkers in childhood asthma. *Pediatr Allergy Immunol* 2018;**31**:44–55.
51. Moore WC, Hastie AT, Li X, Li H, Busse WW, Jarjour NN, et al. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol* 2014;**133**:1557–63. e5.
52. Phipatanakul W, Mauger DT, Sorkness RL, Gaffin JM, Holguin F, Woodruff PG, et al. Effects of age and disease severity on systemic corticosteroid responses in asthma. *Am J Respir Crit Care Med* 2017;**195**:1439–48.
53. Robinson D, Humbert M, Buhl R, Cruz AA, Inoue H, Korom S, et al. Revisiting Type 2-high and Type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy* 2017;**47**:161–75.
54. Hirose K, Iwata A, Tamachi T, Nakajima H. Allergic airway inflammation: key players beyond the Th2 cell pathway. *Immunol Rev* 2017;**278**:145–61.
55. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009;**180**:388–95.
56. Samitas K, Zervas E, Gaga M. T2-low asthma: current approach to diagnosis and therapy. *Curr Opin Pulm Med* 2017;**23**:48–55.
57. Kim CK, Koh YY, Callaway Z. The validity of induced sputum and bronchoalveolar lavage in childhood asthma. *J Asthma* 2009;**46**:105–12.
58. Eller MCN, Vergani KP, Saraiva-Romanholo BM, Antonangelo L, Leone C, Rodrigues JC. Can inflammatory markers in induced sputum be used to detect phenotypes and endotypes of pediatric severe therapy-resistant asthma? *Pediatr Pulmonol* 2018;**53**:1208–17.
59. Agache I, Rogozea L. Asthma Biomarkers: do they bring precision medicine closer to the clinic? *Allergy Asthma Immunol Res* 2017;**9**:466–76.
60. Wagener AH, de Nijs SB, Lutter R, Sousa AR, Weersink EJ, Bel EH, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax* 2015;**70**:115–20.
61. Ullmann N, Bossley CJ, Fleming L, Silvestri M, Bush A, Saglani S. Blood eosinophil counts rarely reflect airway eosinophilia in children with severe asthma. *Allergy* 2013;**68**:402–6.
62. Casciano J, Krishnan JA, Small MB, Buck PO, Gopalan G, Li C, et al. Value of peripheral blood eosinophil markers to predict severity of asthma. *BMC Pulm Med* 2016;**16**:109.
63. Akar HH, Tahan F, Gungor HE. The association of forced expiratory volume in one second and forced expiratory flow at 50% of the vital capacity, peak expiratory flow parameters, and blood eosinophil counts in exercise-induced bronchospasm in children with mild asthma. *Asia Pac Allergy* 2015;**5**:98–102.
64. Tran TN, Khatry DB, Ke X, Ward CK, Gossage D. High blood eosinophil count is associated with more frequent asthma attacks in asthma patients. *Ann Allergy Asthma Immunol* 2014;**113**:19–24.
65. Massanari M, Holgate ST, Busse WW, Jimenez P, Kianifard F, Zeldin R. Effect of omalizumab on peripheral blood eosinophilia in allergic asthma. *Respir Med* 2010;**104**:188–96.
66. van Rensen EL, Straathof KC, Veselic-Charvat MA, Zwiderman AH, Bel EH, Sterk PJ. Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma. *Thorax* 1999;**54**:403–8.
67. Pizzichini MM, Pizzichini E, Clelland L, Efthimiadis A, Mahony J, Dolovich J, et al. Sputum in severe exacerbations of asthma: kinetics of inflammatory indices after prednisone treatment. *Am J Respir Crit Care Med* 1997;**155**:1501–8.
68. Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* 2017;**8**:Cd005603.
69. Dweik RA, Comhair SA, Gaston B, Thunnissen FB, Farver C, Thomassen MJ, et al. NO chemical events in the human airway during the immediate and late antigen-induced asthmatic response. *Proc Natl Acad Sci U S A* 2001;**98**:2622–7.
70. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;**184**:602–15.
71. Malinovschi A, Janson C, Borres M, Alving K. Simultaneously increased fraction of exhaled nitric oxide levels and blood eosinophil counts relate to increased asthma morbidity. *J Allergy Clin Immunol* 2016;**138**:1301–8. e2.
72. Smith AD, Cowan JO, Brassett KP, Filself S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med* 2005;**172**:453–9.
73. Price DB, Buhl R, Chan A, Freeman D, Gardener E, Godley C, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in

- patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med* 2018;**6**: 29–39.
74. Rao DR, Phipatanakul W. An overview of fractional exhaled nitric oxide and children with asthma. *Expert Rev Clin Immunol* 2016;**12**:521–30.
 75. Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev* 2016;**11**:Cd011439.
 76. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991;**325**:1067–71.
 77. Takayama G, Arima K, Kanaji T, Toda S, Tanaka H, Shoji S, et al. Periostin: a novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. *J Allergy Clin Immunol* 2006;**118**:98–104.
 78. Song JS, You JS, Jeong SI, Yang S, Hwang IT, Im YG, et al. Serum periostin levels correlate with airway hyper-responsiveness to methacholine and mannitol in children with asthma. *Allergy* 2015;**70**:674–81.
 79. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007;**120**:S94–138.
 80. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;**367**:1198–207.
 81. Hamelmann E, Szefer SJ. Efficacy and safety of tiotropium in children and adolescents. *Drugs* 2018;**78**:327–38.
 82. Hamelmann E, Bateman ED, Vogelberg C, Szefer SJ, Vandewalker M, Moroni-Zentgraf P, et al. Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. *J Allergy Clin Immunol* 2016;**138**:441–50. e8.
 83. Allen DB. Effects of inhaled steroids on growth, bone metabolism and adrenal function. *Expert Rev Respir Med* 2007;**1**:65–74.
 84. Pedersen S. Do inhaled corticosteroids inhibit growth in children? *Am J Respir Crit Care Med* 2001;**164**:521–35.
 85. van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;**18**:913–8.
 86. Bousquet J, Brusselle G, Buhl R, Busse WW, Cruz AA, Djukanovic R, et al. Care pathways for the selection of a biologic in severe asthma. *Eur Respir J* 2017;**50**.
 87. Abrams EM, Becker AB, Szefer SJ. Current state and future of biologic therapies in the treatment of asthma in children. *Pediatr Allergy Immunol Pulmonol* 2018;**31**:119–31.
 88. Licari A, Castagnoli R, Panfil E, Marseglia A, Brambilla I, Marseglia GL. An update on anti-IgE therapy in pediatric respiratory diseases. *Curr Respir Med Rev* 2017;**13**:22–9.
 89. Kopel LS, Phipatanakul W. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Pediatrics* 2014;**134**(Suppl 3): S179–80.
 90. Deschildre A, Marguet C, Langlois C, Pin I, Rittie JL, Derelle J, et al. Real-life long-term omalizumab therapy in children with severe allergic asthma. *Eur Respir J* 2015;**46**:856–9.
 91. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014;**1**:Cd003559.
 92. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes Jr SJ, Calatroni A, et al. Pre-seasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;**136**: 1476–85.
 93. Pike KC, Akhbari M, Kneale D, Harris KM. Interventions for autumn exacerbations of asthma in children. *Cochrane Database Syst Rev* 2018;**3**:Cd012393.
 94. Generoso A, Muglia-Chopra C, Oppenheimer J. Prospects for monoclonal antibody therapy in pediatric asthma. *Curr Allergy Asthma Rep* 2018;**18**:45.
 95. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;**371**:1198–207.
 96. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;**380**:651–9.
 97. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017;**9**:Cd010834.
 98. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017;**5**:390–400.
 99. Nucala [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2015. Available from: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. Date last accessed: 30 August 2018.
 100. CINQAIR® (reslizumab) [Prescribing Information], Teva Respiratory, LLC Frazer, PA. Available from: <https://www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf>. Date last accessed: 11 November 2018.
 101. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;**3**:355–66.
 102. Bjerner L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest* 2016;**150**:789–98.
 103. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;**388**:2128–41.
 104. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;**388**:2115–27.
 105. Fasenra (Benralizumab) [Prescribing Information], AstraZeneca Pharmaceuticals LP, Wilmington, DE. Available from: https://www.azpicentral.com/fasenra/fasenra_pi.pdf#page=1. Date last accessed: 11 November 2018.
 106. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;**378**:2486–96.
 107. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;**378**:2475–85.
 108. Dupixent (Dupilumab) [Prescribing Information], Regeneron Pharmaceuticals, Inc. Tarrytown, NY. Available from: https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf. Date last accessed: 11 November 2018.
 109. Gønem S, Berair R, Singapur A, Hartley R, Laurencin MFM, Bacher G, et al. Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2016;**4**:699–707.
 110. Farne H, Jackson DJ, Johnston SL. Are emerging PGD2 antagonists a promising therapy class for treating asthma? *Expert Opin Emerg Drugs* 2016;**21**:359–64.
 111. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017;**377**:936–46.