

Severe Asthma in Children

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Abstract

Purpose of Review The aim of this study is to characterize, diagnose, evaluate, and treat severe childhood asthma.

Recent Findings Understanding the occurrence of the physiologic and clinical presentations of childhood severe asthma, the treatment and response may be predicted by biomarkers, but the patient's response is highly variable.

Summary The onset of severe asthma occurs early and is primarily predicted by severity of viral infection and coexistence of the atopic state.

Keywords Severe asthma · Childhood asthma · Biomarkers · Biologic therapy · Pharmacologic therapy

Introduction

Severe asthma in children often begins in the first year of life associated with severe viral illness in a patient with atopic features. The early presence of a Th2 inflammatory pattern is a significant predictor of disease progression. Physiologic abnormalities of asthma occur early in life and remain

persistent. Currently, available treatments have not been shown to provide disease modification.

Natural History of Severe Asthma

Asthma affects nearly 6 million children in the USA approximately 10% of children less than 15 years of age. A total of 5–10% of these children have severe or difficult-to-treat asthma. The medical expenditure for asthma is approximately 10 billion annually with severe asthma accounting for up to 50% of these costs. The National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP 1–2) collected data from 2001 to 2011. The SARP group enrolled 140 children with severe asthma. These children had increased numbers of blood eosinophils, were atopic, and had variable degrees of airflow limitation [1].

A subsequent analysis of the SARP-3 cohort of 709 subjects (187 children) examined the inflammatory and comorbid features of patients with severe asthma [2•]. In the cohort, 41% had no exacerbations, 34% had few exacerbations, and 24% (173) were exacerbation prone (EPA). The participants with a high number of exacerbations had a higher BMI, were on more controller medications, and had lower ACT scores. Regardless of exacerbation history, the children had normal mean FEV1 and FVC measurements. Of note, the children without exacerbations had the highest mean FEV1/FVC ratio (within the normal range). Of the children, 24% with an FEV1 percentage predicted greater than 80% were exacerbation prone. The adults and children with severe asthma had more albuterol reversibility than participants with nonsevere disease. The relationship between exacerbation frequency and measures of type 2 inflammation was

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inconsistent. Elevated blood eosinophils, high BMI, sinusitis, and reflux are highly associated with exacerbation frequency in all models. It appears that the pathophysiological mechanisms contributing to exacerbations were different from those driving asthma severity. The findings raise the question whether EPA is associated with features of airway remodeling such as smooth muscle hypertrophy or basement membrane thickening. These data continue to provide insight into the frequent exacerbation prone asthmatic.

In the TENOR study, 1267 children and adolescents with severe or difficult-to-treat asthma were enrolled over a 3-year period [3]. The study showed that healthcare utilization and disease activity have not been appropriately addressed with the currently available pharmacologic agents. Figures 1, 2, and 3 show that in children 6 to 17, a significant burden of disease is present when there is either 1, 2, or 3 controllers prescribed. There was little extra benefit achieved adding either a long acting beta agonist or a leukotriene receptor antagonist to inhaled corticosteroid. Between 34 and 48% of children had either corticosteroid bursts and unscheduled office visits in the 3 months before the first TENOR study visit. Additionally, asthma exacerbations at the 30 month follow-up visit were associated with consistently very poorly controlled (VPC) asthma in the impairment domain. For children 6 to 11 years, odds ratio (OR) is 6.4 for an exacerbation when one occurred in the previous year, and for adolescents OR 4.9. This confirms a clear association with very poorly controlled asthma and subsequent exacerbations. A leading predictor for exacerbations is having an exacerbation in the previous year. When the impairment domain is analyzed, the use of short acting beta agonist was the greatest predictor for exacerbation and VPC asthma in the TENOR study. The economic burden was significant in these patients with VPC asthma compared to those with not well-controlled (NWC) or well-controlled (WC) asthma. A twofold increase in medical cost was seen in the VPC group. Quality of life was also significantly affected in patients with VPC asthma in patients having three or four asthma control problems compared to no control problems with a greater risk of unscheduled office visits, oral steroid bursts, and hospitalizations. This shows that quality of life is significantly affected by poor asthma control [3].

The U-BIOPRED cohort allows further insight into the effect of poorly controlled asthma in childhood and adolescence [4]. Seven centers in Europe recruited 77 preschool children 1 to 5 years of age and 97 school-age children 6 to 17 years of age receiving respiratory care at general pediatric clinics. The inclusion criteria included ongoing poorly controlled asthma requiring high-dose inhaled corticosteroid and

two other controllers. Mild to moderate school age children and preschool children were also studied. The features that predicted increased asthma burden and decreased quality of life included a low FEV1, exacerbations in the previous year, low Asthma Control Test (ACT), or Children's Asthma Control Test (C-ACT). The children with severe disease had significantly lower quality of life scores across all domains as compared to the mild to moderate patients. Asthma control and airway obstruction were found to be associated with decreased quality of life. The vast majority of these children had positive skin tests to perennial allergens, pollens, and food allergens. In this cohort, 17% had been prescribed omalizumab and 24% were on maintenance oral corticosteroid. FEV1 was not a good discriminator of severity in this cohort, although significant airflow obstruction and bronchodilator responsiveness did occur in the more severe group.

In the Inner City Asthma Consortium (ICAC), 619 children, 6 to 17 years of age, were studied with 41% (254) having difficult-to-control or severe asthma [5]. A distinguishing baseline characteristic compared to patients with mild to moderate asthma was bronchodilator response, ACT or C-ACT below 20, low FEV1/FVC ratio, and elevated rhinitis medication score were major determinates for persistent symptoms. The children with greater bronchodilator response, even in the face of normal spirometric results, had more nocturnal symptoms, increased beta agonist use, exercise limitation and also had a greater number of allergen sensitizations. During the 12-month longitudinal study, the two groups of difficult-to-control and easy-to-control asthma exhibited similarities and differences over time. The difficult-to-control group did not show any trend for improvement in the 1 year despite guideline-based treatments, whereas the easy-to-control group did respond. The difficult-to-control group had higher Fall and Spring exacerbation rates and more daytime and nighttime symptoms in the fall and winter.

Difficult-to-treat, sporadic, severe asthma may in part be related to poor adherence to standard control medications and insufficient avoidance of asthma triggers [6]. Furthermore, other factors that are intrinsic to the patient or present living environment may reduce asthma control. It has been shown that the children with severe asthma and fungal sensitization with early onset disease have higher IgE levels, more maintenance oral corticosteroids, and increased IL-33 levels than allergic children with severe asthma without fungal sensitization [7]. Therefore, the combination of early onset disease with a more turbulent initial course and significant environmental allergy sensitization to cockroach, mouse, and mold may be risk factors for increase in disease activity. Other factors include exposure to outdoor allergens, pollutants, and environmental tobacco smoke.

The cluster analysis of the children in SARP, cluster 1, was early onset of atopic asthma ($N = 32$), and average FEV1% predicted was 84% ($\pm 21\%$) with 18% maximal bronchodilator

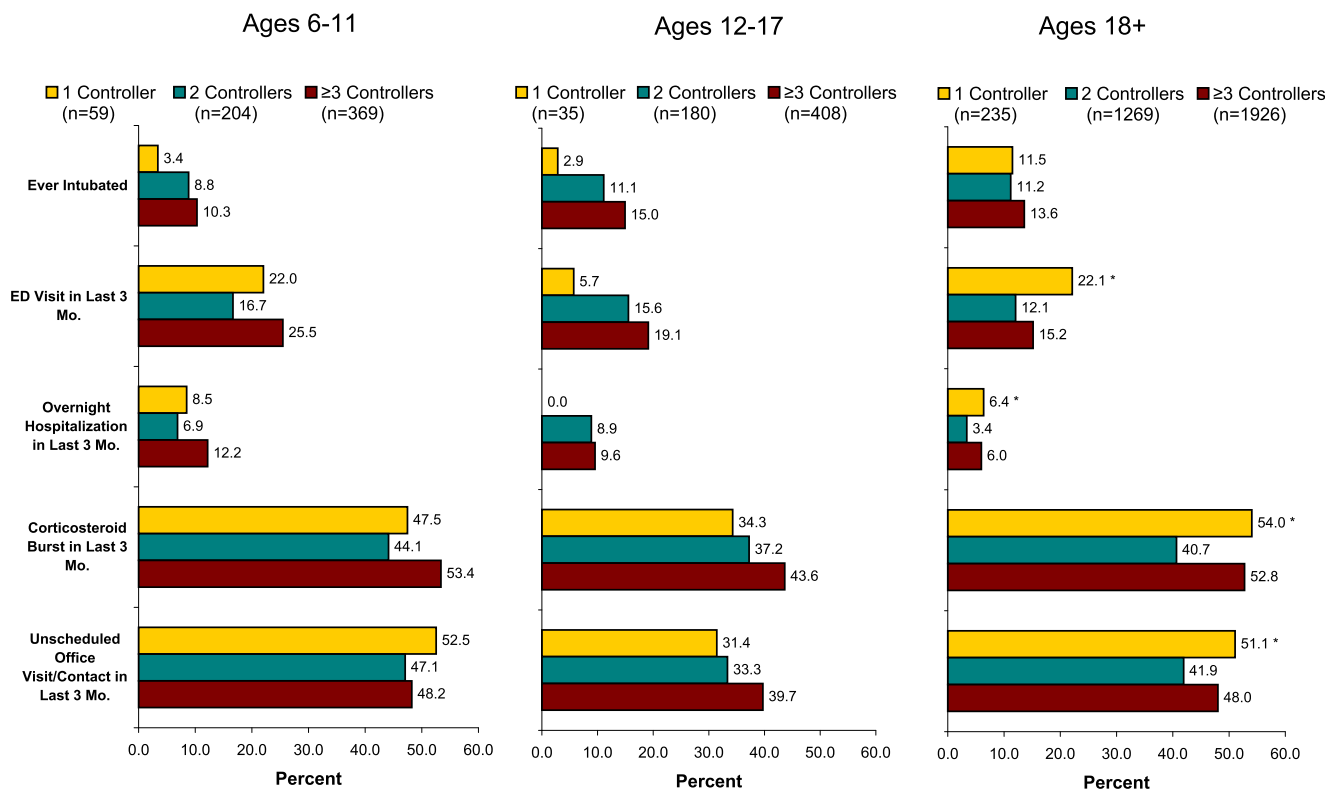


Fig. 1 Rates of HCU by number of long-term controller medications in patients aged 6 to 11 years (*left panel*), 12–17 years (*center panel*), and 18 or more years (*right panel*). Long-term controllers included ICSs, long-acting beta-agonists, leukotriene modifiers, methylxanthines, and cromolyn sodium or nedocromil. No statistically significant differences

were found in rates of HCU by number of long-term controllers in children and adolescents. * $P < 0.01$ for all HCU measures in adults except history of intubation, which was nonsignificant. Published with permission from Chipps et al. [3]

responsiveness. Cluster 2 ($N = 29$) had early onset atopic asthma and advanced airflow obstruction with an FEV₁ of 75% ($\pm 16\%$) with a 20% ($\pm 19\%$) change in FEV₁ after maximum bronchodilatation [8]. This is compared to cluster 3 with later onset symptomatic asthma, and cluster 4 had early onset atopic asthma with normal lung function with maximum

bronchodilator responsiveness of 13% ($\pm 15\%$) and 14% ($\pm 14\%$). It is of note that the children with more significant airflow limitation did not demonstrate hyperinflation or increase in residual volume. The major factors associated with asthma severity and more significant airflow obstruction were atopy and need for multiple controllers. In the Avon longitudinal study of parents and children (ALSPAC) a longitudinal population base birth cohort study with 14,062 liveborn children, a diagnose for asthma was confirmed at 7.5 and 14 years

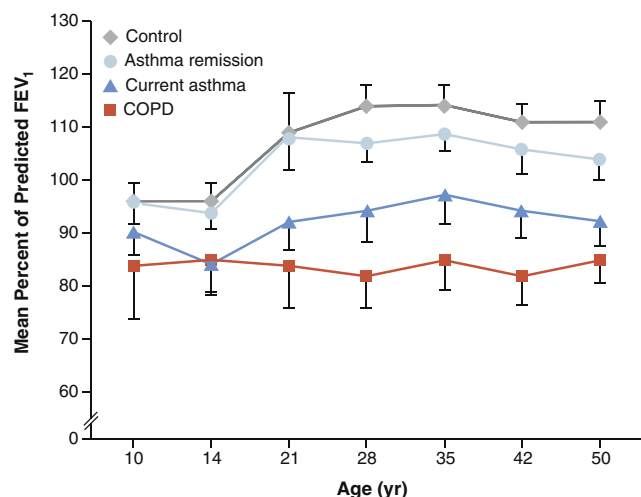


Fig. 2 Percent of predicted FEV₁ in participants followed between the ages of 10 and 50 in the Melbourne Asthma Study [13]. Reproduced with permission from Martinez [13]

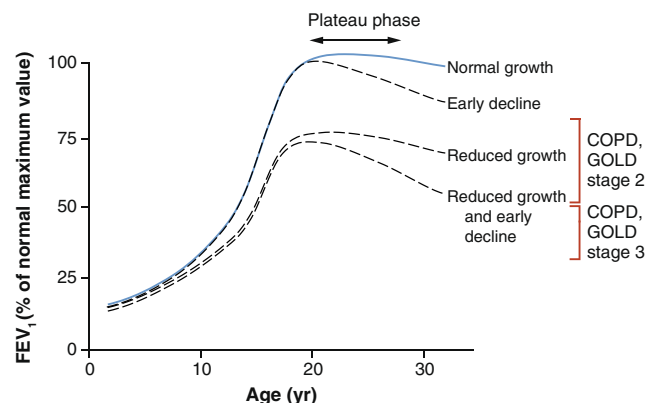


Fig. 3 Longitudinal lung-function trajectories. Reproduced with permission from McGeachie [14••]

of age [9]. Doctor diagnosed asthma determined that at 7.5 years of age and also 14 years of age. Latent class analysis was used to understand the determinants for more persistent wheezing which included FeNO greater than 35 ppb, FEV1/FVC and FEF25–75 decreased. FEV1 was not a major determinant.

Multiple long-term epidemiologic studies have been reported. The Melbourne Asthma Study, which now has had a 50 years follow-up, shows that patients with severe asthma at the first measurement have abnormal FEV1 (83%) that persisted throughout the 50 years follow-up. These patients who had a lower chance of remission (14%) female sex and childhood hay fever characteristics that would predict more persistent disease [10•]. This has also been collaborated with the Dunedin cohort [11] and the Tucson Children's Respiratory Study [12].

The CAMP cohort followed patients from enrollment at age 5 to 12 years, into the third decade of life, with at least annual pre-bronchodilator and post-bronchodilator spirometry showed a significant pattern in patients [14••].

Of the 684 study participants available for analysis in this study, 25% had normal pattern of lung function growth and 75% had highly abnormal patterns. However, 26% had reduced growth and an early decline, 23% had reduced growth only, and 26% had normal growth and an early decline. Lower baseline values of FEV1, smaller bronchodilator response, airway hyper-responsiveness at baseline, and male sex were associated with reduced lung growth in all four comparators. As previously prescribed by Covar, independent of treatment group (budesonide, nedocromil, placebo), 26% of CAMP patients had an accelerated drop in lung function during the study period [15]. Comparing lung function at enrollment, male sex is the most significant predictor of abnormal longitudinal patterns of lung function growth and decline. Identification of trajectory early with FEV1 measurements can identify children and adolescents who are at risk for abnormal lung growth that may lead to chronic airflow obstruction.

Advances/new Applications in Step Therapy

Intermittent High-Dose Inhaled Corticosteroid

The standard treatment for pediatric asthma is to use ICS, but there is growing parental concern about possible long-term effects. There is a small statistically significant difference in height growth seen between low and low to medium doses of ICS in pediatric asthma patients that is independent of the type of ICS used [16]. Potential side effects like this make parents weary about using ICS consistently especially when they feel their child's symptoms are episodic. Many pediatric patients only have symptoms when triggered by a viral illness and will

be symptom-free in between. This has led to the option of using intermittent high-dose ICS. The MIST trial (Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers) found no significant difference between using intermittent high-dose ICS (budesonide 1 mg twice a day) at the onset of respiratory illness compared to daily low-dose ICS (budesonide 0.5 mg nightly) in the number of exacerbations needing oral steroids. Those using the intermittent high-dose regimen were also exposed on average to 104 mg less of budesonide per year than those in the daily low-dose regimen [17]. If a young pediatric patient has episodic asthma symptoms, it may be worth trying high-dose intermittent ICS as it appears comparable to daily low-dose ICS in this patient population. The GINA guidelines still recommend daily low-dose ICS as the initial treatment to control asthma in children less than 5 years of age, but it does say to consider episodic ICS for those children with viral-induced wheezing and interval asthma symptoms [18].

Single Inhaler as Maintenance and Reliever

The updated GINA guidelines from 2015 added low-dose inhaled corticosteroid/formoterol (in the form of low-dose budesonide/formoterol or low-dose beclomethasone/formoterol) to step 3 for adults and adolescents as both a maintenance and reliever medication for patients with more than one exacerbation in the last year [18]. This method is sometimes referred as the Symbicort maintenance and reliever therapy (SMART) strategy or as the single inhaler therapy. The SMART strategy studied 4–11-year olds where budesonide/formoterol 80/4.5 µg daily plus as needed was compared to budesonide/formoterol 80/4.5 µg daily plus terbutaline as needed (fixed combination) versus higher dose budesonide 320 µg daily plus terbutaline as needed (fixed dose budesonide). The patients using the SMART strategy had a longer time to first exacerbation, had lower number of exacerbations needing medical attention, and reduced number of nighttime awakenings [19]. Using a single inhaler for both maintenance and rescue was found to be effective, well-tolerated, and simplified a patient's asthma regimen. Many times patients and parents become confused on which inhaler is their maintenance versus which is their rescue. If they only had to use one inhaler, this would ease their confusion and may make them more compliant with therapy. In 2013, a Cochrane review looked at using the single inhaler therapy and found that those patients using budesonide/formoterol as a single inhaler had fewer exacerbations requiring hospitalizations, ER visits, and oral corticosteroids as well as lower mean daily dose of ICS than those on a fixed dose combination inhaler [20•]. Of note, adding on a LABA as a fixed dose combination inhaler achieves better asthma control than adding it as a separate inhaler [21].

Tiotropium

Tiotropium is a daily long-acting anticholinergic agent that is now recommended at 5 µg as add-on therapy in steps 4 and 5 for those over 18 years of age who have a history of exacerbations [18]. Tiotropium when combined with ICS/LABA in adults was found to increase peak FEV1, through FEV1 and time to first exacerbation. It also was found to reduce the risk of a severe asthma exacerbation by 21% [22]. A phase III trial completed in 12–17-year olds comparing tiotropium 5 µg once daily, 2.5 µg once daily, and placebo when added to ICS maintenance therapy with or without leukotriene receptor antagonist found a greater improvement in lung function with the 5 µg once daily dose [23]. A phase II trial already showed that all dosages of tiotropium (5 µg, 2.5 µg, and 1.25 µg once daily) were well-tolerated in 12–17-year olds [24]. There has also been a phase II trial in 6–11-year olds comparing once daily tiotropium at 5, 2.5, and 1.25 µg to placebo as add-on therapy to maintenance ICS with or without a leukotriene receptor antagonist with all doses showing significant improvement in lung function compared to placebo and all doses being safe and tolerable [25•]. Spiriva Respimat (tiotropium bromide) 1.25 µg, two inhalations once a day for asthma, has been approved for those 6 and older. The age of approval was changed this year based on phase III trial results that have yet to be published. This is the next add-on therapy to consider in patients with uncontrolled asthma despite standard combination therapy.

Acute Exacerbations

Standard of care has been to treat acute exacerbations with a course of systemic steroids, usually prednisolone or prednisone. Dexamethasone is increasingly being used in emergency departments to treat acute exacerbations for its easy one-time dosing and improved patient tolerability. A meta-analysis looking at 0.6 mg/kg oral or 0.3–1.7 mg/kg IM dexamethasone versus 5 day course of 1–2 mg/kg/day of oral prednisone/prednisolone in the emergency department failed to show significant difference between the two therapies with regard to return rates to clinic, ED, or hospitalizations. Dexamethasone also had better patient and parent satisfaction as it was less likely to cause gastrointestinal symptoms [26]. Dexamethasone does not have the bitter taste that some versions of prednisolone have and therefore less likely to be vomited. These findings of dexamethasone being comparable to prednisone in treating acute asthma and being better tolerated in the ED have been reproduced [27].

Biomarkers

An increase in understanding of the heterogeneous nature of asthma has led to the development of asthma phenotypes. As previously mentioned, longitudinal analysis of children and adolescents with asthma has led to clarity in identification of characteristics of the severe pediatric asthmatic patient.

These specific characteristics serve as biomarkers in assisting in asthma severity evaluation, diagnosis of allergies, determination of inflammation in the airways, evaluation of airway hyper-responsiveness, and monitoring the response to particular therapies.

Exhaled Breath Analysis

Many studies have evaluated the role of FeNO in asthma severity and treatment of the severe asthma pediatric patient. Part of the abundance in data is due to the relative ease of technique as well as potential techniques/options for measurement in the very young [28]. FeNO acts as a biomarker of type 2 inflammation generated by stress on respiratory epithelial cells leading to production of NO driven primarily by IL-4 and IL-13 [29]. In children with mild-to-moderate asthma, FeNO was shown to correlate with atopy/IgE levels, serum eosinophilic cationic protein (ECP), blood eosinophils, and bronchial hyper-responsiveness [30]. Additionally, higher levels of FeNO have been shown to correlate with children who are likely to respond to corticosteroid treatment [31]. However, although FeNO levels are often elevated in children/adolescents with allergic asthma, they can also be elevated in patients who are atopic and not asthmatic making FeNO as a sole biomarker for asthma control to be unreliable [32].

Also, used as a guide for asthma management/treatment, per meta-analysis of three pediatric studies, using FeNO measurements as the primary guide in asthma treatment did not improve asthma outcomes [33].

Additional exhaled breath analysis, applicable in the research setting, relates to analysis of volatile organic compounds (VOC) in exhaled air via gas chromatography coupled with mass spectrometry (GC-MS). Metabolic compounds originating from the upper/lower respiratory tract are profiled via GC-MS. VOC analysis has been able to predict subsequent exacerbations in children with asthma [34]. VOC analysis has also been able to predict response to steroids in patients with asthma more accurately than FeNO or sputum eosinophils [35].

Blood Analysis

Performing blood cell counts can provide significant information in identifying asthma phenotypes. Many studies of adults with asthma have demonstrated a correlation between high peripheral eosinophilia and higher total IgE, more asthma

exacerbations, lower FEV1, and response to corticosteroid therapy [36, 37]. In pediatric asthma, high eosinophil counts have been shown to correlate with asthma severity as well as corticosteroid response in the pre-school pediatric subgroup [38]. For adults with severe asthma, blood eosinophil counts when above 450 cells/ μ L correlated with elevated sputum eosinophil $>2\%$ [39, 40]. Those adults with severe asthma and both high sputum and blood eosinophils also have higher exacerbation rates. Adults with normal eosinophil counts (<400 cells/ μ L) but elevated sputum eosinophils ($>3\%$) have higher exacerbation rates compared to those with normal sputum/blood eosinophils [41•]. Moreover, in adults, eosinophils counts by themselves can be misleading in predicting exacerbation risk. In pediatric asthma, blood eosinophils have not been shown to correlate well with eosinophil burden in airways [42]. Hence, larger pediatric prospective studies need to be completed to assess the usage of both eosinophil blood counts and FeNO together for asthma monitoring, severity, and prediction of exacerbations.

Serum total IgE has been used as a marker for diagnosis of atopic asthma. Evidence of allergen-specific IgE levels, for inhalant aeroallergens, has been used as criteria in clinical diagnosis of atopic asthma for research purposes. Neither total IgE nor allergen-specific IgE levels have been shown in children to predict asthma exacerbation risk, severity, lung function, or symptoms. In terms of treatment, allergen avoidance driven by allergen-specific IgE levels can be useful; however, determination of allergen sensitivity by allergy skin prick test has been shown to be more specific. Demonstration of allergen-specific IgE levels does not guarantee activation of immune effectors cascade and production of symptoms with exposure. Allergen-specific IgE levels represent a possible allergen source but may not be very specific as potential for cross-reactivities exist. Dosage of omalizumab, humanized monoclonal IgG1 κ which binds to the Fc region of IgE, a treatment for severe allergic asthma, is dependent on total IgE levels and body weight. However, it has been shown that this level and dosage do not correlate with treatment response [43].

Periostin is a matricellular protein that is expressed in adult and fetal tissues and has been found to play a role in development of bone, tooth, heart valves, and also the eosinophilic inflammatory process of asthma [44]. Type 2 driven airway inflammation includes production of IL-4, IL-13, and also TGF- β which stimulate epithelial cell and fibroblast production of periostin [45]. Additionally, IL-4 and IL-13 cytokines also stimulate eosinophils to produce periostin. Studies in adult asthma patients demonstrate that there are elevations in plasma periostin in eosinophilic asthma [46]. Periostin correlates with response to anti-IL-13 biologic therapy where there was increased expression of epithelial cells and production of IL-4 and IL-13 in the airways [47, 48]. However, in children, periostin has yet to been shown to be a reliable biomarker. Baseline periostin levels tend to be higher, likely a result of

bone growth, likely a confounding variable explaining inconsistent reliability of periostin as biomarker in pediatrics [49]. Mildly increased levels of periostin in children with asthma versus healthy controls have been seen, but not in all ages [50]. In a study looking at children with moderate-severe asthma, there were no correlations observed between serum periostin and FeNO, total IgE, and blood eosinophil counts [51]. Dipeptidyl-peptidase-4 (DPP-4), like periostin, is also upregulated by IL-13. Studies in adult asthma patients have shown elevations of DPP-4 in subsets of severe asthma patients who improved in FEV1 with anti-IL-13 therapy in those with elevated DPP-4 levels [52]. More studies are needed to assess the potential role of DPP-4 in children.

These biomarkers have focused on the key mediators contributing to type 2 pathway and eosinophilic airway inflammation in asthma. As described before, this pathway refers to the release of type 2 cytokines IL-4, IL-5, and IL-13 from not only T_H2 cells but also group 2 innate lymphoid cells (ILC2). However, not all asthma is driven by this type 2 pathway, and the heterogeneous nature of asthma suggests the need for further research in identification and study of potential biomarkers for other asthma phenotypes. One example is YKL-40, a chitinase-like protein, thought to be involved in airway remodeling and fibrotic lung disease. The exact mechanism of action is not completely clear, but it has been found to be elevated in children and adults with severe asthma, as well as in those with reduced lung function [53–55]. Further identification of additional biomarkers on non-type 2 inflammatory pathways, as well as better understanding of the relationship between them will allow for a greater precision-targeted approach to treatment. Multiple biologic treatments have been approved targeting the type 2 inflammatory pathway. However, results from U-BIOPRED project suggest a different phenotype in comparison of adults versus children/adolescents with severe asthma [4, 56]. Moreover, caution should be used in usage of biomarkers alone in decision of treatment. Instead, a comprehensive approach including biomarkers with patient demographics, history, symptoms, lung function, and exacerbation risk should all be considered when creating an optimal treatment plan.

Role of Biologic Therapy

The previous section reviewed advances in step therapy for the treatment of pediatric asthma. Despite these options for add-on therapy, a significant percentage of children continue to have uncontrolled severe asthma. Previously discussed biomarkers have been shown to help not only predict symptoms, severity, and exacerbation risk but also response to treatment. Biologic therapies targeting inflammatory mediators, primarily involved in the type 2 pathway, can help in the treatment of severe asthma. Two have currently been approved for use in

younger children (omalizumab) and adolescents (mepolizumab) which will be discussed here in detail.

Mepolizumab is a recombinant, humanized IgG1 κ monoclonal anti-IL-5 antibody, approved in 2015 as add-on therapy for those age 12 years and older with severe eosinophilic asthma. Mepolizumab prevents IL-5 binding to the α -subunit of IL-5 receptor complex found on the eosinophil surface. This prevents the differentiation, recruitment, activation, growth, and survival of eosinophils [57]. Eosinophils have been shown to play a key role in determining asthma severity, exacerbation rate, and response to corticosteroid therapy. Studies have shown efficacy of mepolizumab when used for patients with severe eosinophil-driven asthma as demonstrated by sputum eosinophil counts and blood eosinophil levels. Mepolizumab, in patients with sputum eosinophilia >3%, reduces exacerbation risk in those who have suffered at least two exacerbations in the previous year. In that same study, there was no effect of mepolizumab on asthma symptoms, bronchial hyper responsiveness, nor improvement in FEV1 [58]. However, other studies have demonstrated improvement in FEV1 and oral-corticosteroid sparing effects with use of mepolizumab in patients with eosinophilic asthma [59–61]. Another study showed mepolizumab to also reduce asthma exacerbation rates in use in patients with history of asthma exacerbations despite high-dose ICS use and peripheral eosinophilia (at least >150 cells/ μ L) [59]. Interestingly, mepolizumab's efficacy was demonstrated irrespective of patient's level of atopy [62]. Also, low-dose mepolizumab (100 mg SC) did not suppress sputum eosinophil count in 50% of patients, which was associated with relatively less reduction in exacerbation risk and steroid sparing effects compared to when sputum eosinophil count was reduced [63]. Safety studies show mepolizumab to be generally well-tolerated. Adverse reactions seen in 3% receiving mepolizumab 100 mg included headache, back pain, fatigue, muscle spasms, urinary tract infection, among others. Safety warnings include risk of hypersensitivity reaction and serious adverse event of herpes zoster infection (two patients in controlled trials). Caution is recommended although no clear association has been demonstrated, regarding mepolizumab's potential role in altering the immune response to helminth infections given its mechanism of action on eosinophils [57].

Omalizumab was approved in 2016 for use as add-on therapy in children ages 6 and older with severe atopic asthma. Atopic asthma, demonstrated by a positive skin test or evidence of in vitro reactivity to a perennial aeroallergen, is driven by the development of a type 2 inflammatory response secondary to allergen exposure/presence in the airway. Allergens drive the polarization to T-helper 2 cells, leading to recruitment and activation of mast cells, eosinophils, basophils as well as B cell immunoglobulin class-switching and generation of allergen-specific IgE antibody [64–66]. Omalizumab, a humanized monoclonal anti-

immunoglobulin E (IgE) antibody, is able to attach to the Fc receptor of freely circulating IgE. By doing so, it blocks the binding of free IgE to cell surface receptors of mast cells, basophils, and antigen presenting cells. Decreasing levels of free IgE are associated with IgE receptor downregulation on cells, and subsequent decrease in IgE-mediated immune activation and inflammation. Additionally, omalizumab's immunomodulatory attributes have been shown to modify long-term effects of allergen-induced airway tissue remodeling and presence of type 2 inflammation [67, 68]. Numerous observational studies have demonstrated a strong atopic phenotype in children with severe asthma. Understanding this atopic phenotype, the role of allergen exposure and development of allergen-specific IgE antibody and subsequent development of airway type 2 inflammation makes IgE a practical target for treatment. Numerous clinical studies have demonstrated efficacy of omalizumab in the pediatric population. In 2001, a study showed omalizumab allowed for a fixed corticosteroid dose reduction in children 6–12 years of age with moderate to severe atopic asthma. A secondary outcome was reduction in asthma exacerbations [69]. A 24-week open-label extension of this study demonstrated long-term effectiveness of omalizumab with maintenance of reduced fixed corticosteroid dose [70]. An immunomodulatory role of omalizumab was demonstrated, and FeNO levels were found to be reduced [71]. In 2009, a study was designed to look at omalizumab effect on asthma exacerbations in children aged 6–12 years of age with moderate to severe atopic asthma who were uncontrolled on medium-high-dose ICS/LABA and possibly other controllers. On a fixed corticosteroid dose, omalizumab was shown to reduce asthma exacerbations at 24 and 52 weeks [72]. A 60-week study by ICAC (National Institute of Allergy and Infectious Diseases, Inner-City Asthma Consortium), called ICATA (ICAC Inner-City Anti-IgE therapy for Asthma), studied the effect of omalizumab on asthma symptoms when added to therapy for children, adolescents, and young adults with atopic asthma. There was an improvement in asthma symptoms, with secondary outcomes demonstrating reduction in children with >1 exacerbation and reduction of inhaled corticosteroid dose required for asthma control. Post hoc analysis demonstrated reduction in seasonal peaks in exacerbations which included those peaks outside of pollen season (Fall). This suggests an additional immunomodulatory effect of omalizumab outside of IgE [73]. The ICAC Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study compared the use of omalizumab versus inhaled corticosteroid boost versus continuing guideline therapy in prevention of fall seasonal exacerbations in children 6–17 years of age. Children requiring at least 500 μ g of fluticasone equivalence twice daily were found to benefit most from omalizumab [74]. In 2009, the European Medicines Agency (EMA) approved the use of omalizumab as add-on therapy in children (ages 6 and older). Subsequent

European observational studies showed benefit of omalizumab in pediatric asthma. One observational study in France showed add-on therapy with omalizumab after 1 year improved asthma control, and 72% reduction in severe exacerbation rates decreased mean ICS dose and reduced healthcare utilization in children and adolescents 6–18 years of age, who were strongly atopic and uncontrolled on high-dose ICS maintenance therapy [75]. At year 2, there was an overall continued benefit with use of omalizumab, also with 83% reduction in mean rate of exacerbations. In terms of adverse effects, the study also showed that omalizumab was well tolerated, with anaphylaxis reported in only 1 patient (later deemed unrelated to omalizumab) [76•]. A UK study showed a corticosteroid-sparing effect of omalizumab on children ages 5–12, who required oral corticosteroids for maintenance of their asthma [62]. Omalizumab appears to be very well tolerated with most common adverse events reported to be headache, sinusitis, respiratory tract infection, and rarely hypersensitivity reactions. The 5-year epidemiologic study of omalizumab, EXCELS (evaluating clinical effectiveness and long-term safety), evaluated the serious adverse events (including malignancy) in patients older than 12 years of age [77]. There was no significant increase in malignancy versus placebo, and thus, the FDA determined that given the overall significant potential significant benefit in children, omalizumab was approved for patients 6–12 years of age [78].

Omalizumab and mepolizumab are currently the only two biologics approved for use in children and adolescents. Another biologic has been approved for use in adults ages 18 and over, reslizumab, a humanized IgG4κ monoclonal anti IL-5 antibody that is administered intravenously, dosed by weight. Other biologics targeting the type 2 inflammatory pathway are currently being studied, in phase 3 trials, including benralizumab (anti-IL-5), dupilumab (anti-IL4 receptor alpha subunit), lebrikizumab (anti-IL-13), and tralokinumab (anti-IL-13). Studies involving these biologic drugs have shown mixed efficacy in meeting primary outcomes. However, study design and use of different biomarkers in identification of specific patients for particular biologic treatments may have played a role. Going forward, a comprehensive evaluation of the pediatric patient, including use of biomarkers, will be useful in phenotype-driven treatment of the severe pediatric asthma patient.

Conclusion

There remains a significant need for disease modification in childhood severe asthma. There is currently no validated strategy that will change the natural course of childhood severe asthma. This remains a significant unmet need.

Compliance with Ethical Standards

Conflict of Interest Dr. Chipps reports personal fees from AstraZeneca, Boehringer Ingelheim, Circassia, Genentech Novartis, and Teva. Drs. Parikh and Maharaj declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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