

Severe Asthma in Childhood



Angela Marko, DO^a, Kristie R. Ross, MD, MS^{b,*}

KEYWORDS

• Severe asthma • Children • Phenotype • Management

KEY POINTS

- Severe asthma in childhood is a heterogeneous condition, but is broadly defined as asthma that requires a high level of therapy to achieve control.
- Asthma phenotypes and endotypes are important to stratify clinical features, underlying pathophysiological mechanisms, and treatment responses and are essential to guide future therapeutic development.
- Management of a child with severe asthma requires a detailed multidisciplinary assessment.

INTRODUCTION

Childhood asthma, characterized by airway inflammation, hyperresponsiveness, and variable airflow obstruction, affects 8.4% of all children younger than 18 years in the United States.^{1,2} Although many children with asthma respond well to standard therapies, such as short-acting bronchodilators and daily inhaled corticosteroids (ICSs), a substantial minority do not.³ Severe asthma in childhood is a heterogeneous condition, but is broadly defined as asthma that requires a high level of therapy to achieve control.^{4,5} The prevalence of severe asthma in children is estimated to be approximately 5% to 10% of the total asthma population.⁴ However, the burden on these children and the health care system is quite high, with the annual cost of caring for these children estimated to be more than half of all asthma-related health care expenditures, primarily due to much higher resource utilization.⁶

The definition of severe asthma proposed in the American Thoracic Society (ATS) and European Respiratory Society (ERS) guideline document does not differ among

Dr K.R. Ross reports research grants to her institution from the National Institutes of Health and the Ohio Department of Jobs and Family Services relevant to the current work, nonfinancial support from TEVA, Glaxo Smith Kline, Boehringer Ingelheim, and Astra Zeneca for the conduct of clinical studies related to the current work, and grants for the conduct of clinical trials from Jazz not related to the current work. Dr A. Marko has no conflicts to disclose.

^a Division of Pediatric Pulmonology, University Hospitals Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, Cleveland, OH 44106, USA; ^b Division of Pediatric Pulmonology, University Hospitals Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, OH 44106, USA

* Corresponding author.

E-mail address: Kristie.ross@uhhospitals.org

Immunol Allergy Clin N Am 39 (2019) 243–257

<https://doi.org/10.1016/j.iac.2018.12.007>

0889-8561/19/© 2018 Elsevier Inc. All rights reserved.

immunology.theclinics.com

children, adolescents, and adults, apart from age-specific thresholds of ICS dose that meet the designation of high-dose treatment.⁴ Children and adolescents who either remain uncontrolled when treated with high-dose ICS plus a second controller, systemic corticosteroids for more than 50% of the year, or a biologic therapy are defined as having severe asthma. Lack of control is defined broadly; a patient is considered to be uncontrolled if he or she has at least 1 of the following:

1. A high symptom burden using the Asthma Control Questionnaire or the Asthma Control Test
2. Two or more exacerbations requiring oral corticosteroids in the previous year
3. One or more hospitalization, intensive care unit stay, or episode requiring mechanical ventilation in the past year
4. Airflow limitation (reduced forced expiratory volume in 1 second [FEV₁]/forced vital capacity (FVC) ratio with FEV₁ <80% predicted) following a bronchodilator hold

Children who are controlled while on high-level therapies but lose control with attempts at tapering also meet criteria for severe asthma.

Unlike other chronic conditions that can be staged or graded using objective testing, the definition of severe asthma is based on a determination that the disease is refractory to treatment. This requires that medications are prescribed and taken correctly, comorbid conditions that can influence response to therapy have been evaluated and managed, and that alternative diagnoses that may mimic asthma but would not respond to therapy have been considered. From a practical standpoint, these steps are best accomplished by specialist evaluation and management before making the diagnosis of severe asthma, as suggested in the ATS/ERS guidelines.⁴ Approximately half of children referred for severe asthma have an alternative or comorbid diagnosis and/or modifiable factors that when addressed reduce asthma severity.⁷

Much of the work showing the importance of a multistaged and interdisciplinary approach to the child with difficult asthma has been done in the context of universal access to health care.^{8,9} In the United States, where a significant proportion of asthma care for some populations is delivered in the emergency room setting,¹⁰ the distinction between asthma that is difficult to treat due to comorbid and/or modifiable factors and severe treatment refractory asthma is important at the population health level, but may be challenging to address at the individual patient level.

It is also worth highlighting that many of the children who die from an asthma exacerbation do not necessarily meet the guideline definition of severe asthma, but few would argue that fatal and near fatal asthma represent a severe form of the disease. Children who die from acute asthma are likely a heterogeneous population, ranging from children who have been undertreated because of poor access to care or underrecognition of symptoms, children with high exposures to irritants and/or allergens, children who have severe infections, and children with inherent treatment-refractory severe asthma. The strongest risk factor for a severe exacerbation is a past severe exacerbation,^{11,12} suggesting exacerbation-prone asthma may be a distinct phenotype.¹³

EPIDEMIOLOGY

Although there is heterogeneity in severe childhood asthma, more than two-thirds of children with asthma have allergic sensitization.¹⁴ Early sensitization to foods and aeroallergens is an important determinant of persistent asthma by school age.^{15,16} Several studies have shown that atopy is increased in children with severe asthma compared with mild asthma,¹⁷ in contrast to adults in which the opposite pattern is seen. Allergic sensitization also plays an important role in asthma exacerbations,

best exemplified by the ability of anti-immunoglobulin (Ig)E to reduce the burst of exacerbations seen in children in early fall.¹⁸

In addition to atopy, male sex,¹⁹ maternal or paternal history of asthma,²⁰ preterm birth,²¹ overweight/obesity,²² minority race,²³ and socioeconomic and geographic factors^{24,25} are all well-established risk factors for childhood asthma. There are conflicting reports in the literature with respect to these risk factors and asthma severity and response to treatment, likely due to important interactions with genetic background. For example, in the Severe Asthma Research Program (SARP) III cohort, children with severe and nonsevere asthma were similar in terms of race, sex, and body mass index,¹⁴ whereas earlier pediatric SARP cohorts found nonwhite children were more likely to be categorized as severe.²⁶ Racial and economic disparities and other social determinants of health are important contributors to health care utilization and asthma-related morbidity in the United States^{25,27–31}; whether there are intrinsic differences in asthma severity due to these factors has yet to be determined. However, the impact of adverse life experiences and other prenatal and perinatal exposures more common in poor and minority children on lung development and asthma suggest that there may be lasting biological effects.^{32–35}

PATHOPHYSIOLOGY

Asthma is characterized by airway hyperreactivity, obstruction, and inflammation. Hallmarks of pulmonary physiology in severe asthma include structural abnormalities that affect airway mechanics, including airflow, airway resistance, air trapping, lung elastic recoil, and bronchial hyperresponsiveness.⁴ Many adults with severe asthma are characterized by marked airway obstruction that may be “fixed” (ie, not fully reversible with bronchodilators), particularly in those with early-onset atopic disease.³⁴ Children in the SARP, who were largely atopic and by definition had childhood-onset disease, had evidence for some airway obstruction but it was much less severe than that seen in adults.⁵ Bronchodilator responsiveness was also largely preserved even in children with other features of severe asthma,⁵ suggesting the development of fixed airway obstruction generally occurs after childhood. Children in the more severe phenotypes in the SARP were more likely to have bronchial hyperresponsiveness and air trapping.^{5,6} Whether children with severe disease and early airway obstruction will go on to become adults with moderate to severe fixed airway obstruction is an open question, although there are studies to suggest this progression can occur.^{26,36} Decreased lung recoil is considered an important determinant in airflow limitation, as this contributes to airway narrowing.³⁷ The exact mechanism for this is unknown, but remodeling of the airway outer wall and an increased proportion of abnormal alveolar attachments has been reported in patients with fatal asthma.³⁸ Abnormalities in structural airway cells also contribute to abnormal inflammation and airway mechanics. Early thickening of the reticular basement membrane (RBM) has been described in children with severe asthma.³⁹ Other components of airway remodeling observed in children with severe asthma include larger smooth muscle area, increased MLCK expression (protein involved in smooth muscle contraction), shorter distance between smooth muscle and RBM, and increased density of the vascular network.⁴⁰ Patients with severe asthma also have been observed to have increased transforming growth factor (TGF)- β as well as alterations in collagen deposition.^{40,41} It remains unclear if there is a direct link between airway remodeling and airway inflammation, especially in children with severe disease.^{39,40}

Airway inflammation is a consistent feature of asthma. The dominant cell type found in the airways can be used to characterize airway inflammation, and in adults with

severe asthma, the distinction between eosinophilic, neutrophilic, and paucigranulocytic disease may inform treatment response.⁴¹ Although some studies have shown associations between the dominant cell type in bronchoalveolar lavage fluid and endobronchial biopsies in children and a particular phenotype of severe asthma,^{42,43} others have not.^{42,44} Molecular phenotypes have also been difficult to define in severe childhood asthma.^{44,45} The lack of stability of cellular inflammation in children⁴⁶ and the challenges in assessing it limit the clinical use.^{42,43,45,47,48}

With evidence mounting that an imbalance between Th1 and Th2 adaptive immunity is not sufficient to explain the development of childhood asthma or the severe presentation of childhood asthma, and the recognition of the important role viral infections play in the inception of childhood asthma and during exacerbations, there is intense study of immune dysregulation in asthma outside the classic Th2 paradigm. Areas of interest that may inform the development of new therapies to meet this high unmet need include airway macrophage dysfunction,⁴⁴ oxidative stress,^{49,50} profibrotic signaling including TGF- β 1 expression and activation,⁵⁰ nonallergic inflammation including tumor necrosis factor- α ,⁴⁶ impaired or altered response to viral infections,^{44,49,51} and alterations in the microbiome.⁵⁰

CLINICAL FEATURES

Taken as a whole, children with severe asthma are generally atopic with at least some evidence for eosinophilic airway inflammation.^{5,52} Despite these generally shared features, other characteristics of severe childhood asthma are heterogeneous, with mismatch between domains of impairment and risk.⁵³ The clinical characteristics, or phenotypes, of severe asthma have been described using both hypothesis-driven and unsupervised approaches.^{4,52,54–61} Cluster analysis of children with severe and nonsevere asthma enrolled in the cross-sectional SARP showed children aggregated into 1 of 4 clusters:

1. Early-onset atopic with normal lung function
2. Early-onset atopic with mild airflow limitation
3. Early-onset with advanced airflow limitation
4. Later-onset with normal lung function²⁶

Clusters 3 and 4 had high proportions of children with severe asthma using ATS-ERS criteria. Health care utilization was high in all clusters, but children in clusters 3 and 4 had more unscheduled visits for acute symptoms and more frequent courses of systemic corticosteroids. Separate analysis of children enrolled in the longitudinal Childhood Asthma Management Program (CAMP) found 5 clusters of childhood asthma differentiated by atopic burden, degree of airway obstruction, and history of exacerbations.⁵² Although there was 1 cluster characterized as “low” atopy, more than 75% of children in this cluster had positive skin tests. The long-term follow-up data available in CAMP allowed researchers to show the stability of cluster assignment over time, which has not yet been done with the SARP clusters. Children assigned to clusters 4 and 5 (the most severe clusters) had the highest risk for exacerbations during prospective follow-up. Investigators also showed some evidence that phenotype predicted treatment response in the randomized clinical trial portion of CAMP, in which children were randomized to daily budesonide, nedocromil, or placebo. Children in the less severe clusters 1 to 3 responded best to budesonide; however, children in cluster 4 responded better to nedocromil than either budesonide or placebo, and children in cluster 5 had equal response to budesonide, nedocromil, and placebo.⁵² Others have shown that assigning phenotype using the SARP cluster definitions may also help predict response to therapy in clinical trials, with children assigned to clusters 3

and 4 having more limited response to treatments across several studies in the National Heart Lung and Blood Institute's (NHLBI) Childhood Asthma Research (CARE) Network.⁵⁵ Work is under way now to extend phenotype analyses to include underlying biological mechanisms, known as endotypes, that may help better target therapies.^{44,52,56–64} The NHLBI recently funded the Precision Interventions for Severe and/or Exacerbation Prone Asthma (PreclSE) Network to study targeted treatments in adults and adolescents with severe asthma using these concepts.

Differential Diagnosis and Diagnosis Confirmation

Evaluating severe asthma in children requires a comprehensive approach, beginning establishing that asthma is the most likely cause of symptoms using a comprehensive history, physical examination, and noninvasive testing. Confirming the presence of classic triggers (viral infections, play/exercise, allergens, irritants), typical symptom patterns and response (worse at night, responsive to bronchodilators and previous trials of ICS or other asthma controller medications), and lack of symptoms and signs suggesting disease other than asthma (eg, productive cough, breathlessness without cough, recurrent sinopulmonary or other infections, failure to thrive, clubbing) are important steps. Assessments of the home and school environment, family history, and for comorbid conditions that may modify response to treatment are also important early steps. Multiple studies have shown high rates of alternative diagnoses in children evaluated using comprehensive approaches^{57,58}; therefore, it is important that clinicians maintain a high index of suspicion for conditions that may masquerade as severe asthma (**Box 1**). Assessment of adherence to prescribed medications and the self-management plan include regular use of controller medications, adequate device

Box 1

Conditions that may mimic asthma

Tracheomalacia/bronchomalacia
 Oropharyngeal dysfunction and aspiration
 Retained foreign body
 Vocal cord dysfunction or dysfunctional breathing
 Extrinsic airway compression
 Congenital airway anomaly
 Airway masses/tumors
 Immune deficiency
 Primary ciliary dyskinesia
 Childhood diffuse lung disease
 Suppurative lung disease (non-cystic fibrosis bronchiectasis, chronic bacterial bronchitis)
 Anxiety/panic disorder
 Chronic lung disease of prematurity
 Pulmonary vascular disease
 Pulmonary eosinophilic syndrome
 Allergic bronchopulmonary aspergillosis
 Hypersensitivity pneumonitis
 Obliterative bronchiolitis

technique, avoidance of triggers when possible, and the ability to problem solve during loss of asthma control and exacerbations are also key steps.^{9,58,59}

Spirometry is used to confirm reversible airflow limitation. Testing should include both inspiratory and expiratory loops before and after bronchodilator therapy to assess for presence of reversibility and to help evaluate for upper airway obstruction (eg, vocal cord dysfunction). Ideally, this should be done in the absence of any recent short-acting or long-acting bronchodilators to best assess responsiveness.^{4,59} Spirometry is ideally done before initiation of controller therapies, but as children are frequently not referred for testing before initiation of ICS, the clinical context should be considered in interpretation. Children with severe asthma may have normal lung function and may not show reversibility to bronchodilators on spirometry when well.^{5,26,60} Bacharier and colleagues⁵² reported that FEV₁% predicted did not differ with asthma severity; however, FEV₁/FVC decreased as asthma severity increased. There are also age-related diagnostic challenges in children younger than 6 years. With proper coaching and practice, pulmonary function tests may be possible in young children, although limited reference data exist for this age group.⁶¹ Given the very high prevalence of atopy in children with severe asthma, testing for allergic sensitization with either skin prick testing or allergen-specific IgE should be done.^{54,62} Fig. 1 presents a framework for the consideration of additional testing when clinically indicated in challenging or atypical cases.^{4,59}

MANAGEMENT

International guidelines recommend a stepwise approach to the management of asthma in children and adults.^{54,62} As discussed previously and described in these guidelines, assessment of adherence to the current treatment plan and for modifiable

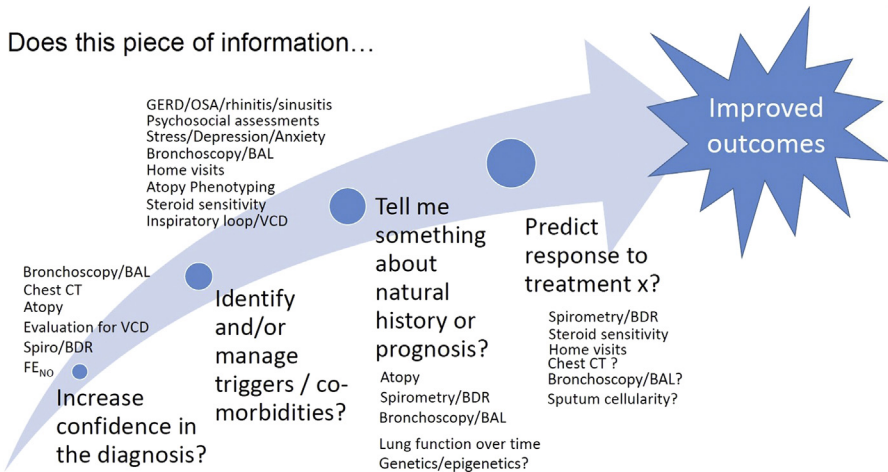


Fig. 1. Framework for the diagnostic and monitoring approach to the child with severe asthma. Evaluation should be directed based on the child's specific symptoms and signs, with consideration of the potential risks. Advanced diagnostic testing may be helpful in establishing the diagnosis of asthma or an alternative diagnosis, identifying modifiable factors that may impact response to therapy, provide prognostic information, or predict response to specific treatments. BAL, bronchoalveolar lavage; BDR, bronchodilator reversibility; CT, computed tomography; FE_{NO}, fractional exhaled nitric oxide; GERD, gastroesophageal disease; OSA, obstructive sleep apnea; VCD, vocal cord dysfunction.

factors limiting the effectiveness of treatment is recommended before escalation of therapy.^{8,62,63} Work in the United Kingdom and by others makes a distinction between difficult-to-treat asthma in which modifiable factors such as adherence, environmental conditions, and comorbid conditions (shown in Fig. 2) impact response, and asthma that is intrinsically refractory to currently available therapies. Much of this work has been done in the setting of universal access to care.^{8,59,64} In environments in which the ability to modify social determinants of health is limited by system financial issues, distinguishing between difficult-to-treat and therapy-resistant asthma is important but may be challenging. Advocacy efforts to impact health policy are critical in this regard. A detailed discussion on adherence monitoring and management, the role of the environment, and the approach to assessment and management of comorbidities (see Fig. 2) (see Carolyn Kercsmar and Cassie Shipp article's, "[Management/Comorbidities of School-Aged Children with Asthma](#)," can be found elsewhere in this issue). The role of each of these steps is particularly important in children with severe asthma, given the potential for adverse effects as therapies are escalated.

After assessment as outlined previously, treatment with high-dose ICS plus a long-acting beta-agonist, leukotriene modifier, theophylline, biologic therapies, and/or prolonged use of oral corticosteroids are used in children with severe asthma to achieve control.^{4,54,65} Treatment responses vary substantially, and the approach to personalized therapies is covered in detail in the article by Guilbert and Pajor, elsewhere in this issue. Assessment of steroid responsiveness and partnering with the child and family to understand the treatment goals they identify as most important may be helpful. Bossley and colleagues⁶⁶ demonstrated that complete response to systemic steroids was rare, with 72% determined to be partial responders and 15% nonresponders, supporting the concept of disease heterogeneity of the disease and the importance of determining treatment response across domains that include symptoms, lung function, exacerbations, and airway inflammation.

In cases in which there is minimal-to-no steroid response or concerns for adverse effects from steroid use, the use of anticholinergics and biological agents should be

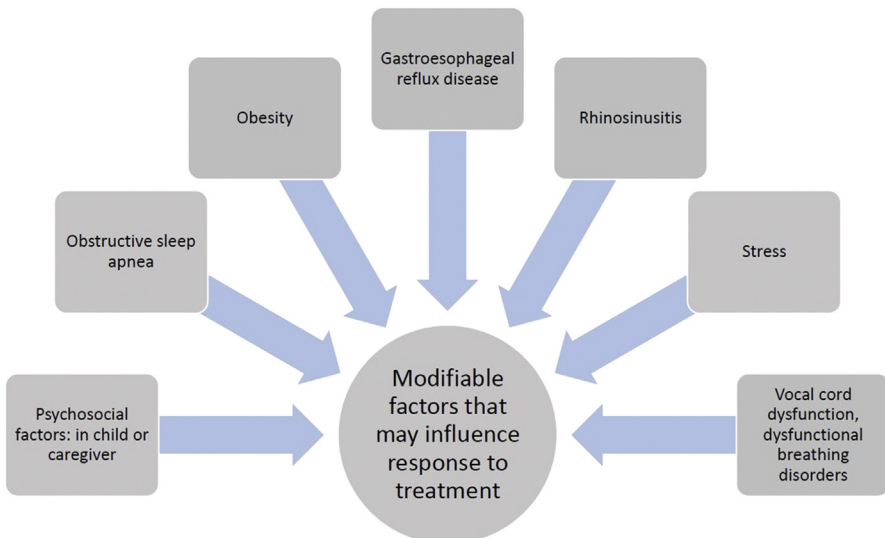


Fig. 2. Comorbid conditions that may influence response therapy and, when addressed, may distinguish difficult-to-treat asthma from asthma that is intrinsically refractive to therapies.

considered.^{4,59,67} Tiotropium is a long-acting anticholinergic used as an add-on therapy in moderate-to-severe asthma that has been approved for use in those 6 years and older. A recent systematic review demonstrated that once-daily tiotropium was efficacious and well tolerated as an add-on medication in school-aged children with symptomatic asthma.⁶⁷ In addition to this, new biological agents provide a more phenotype/endotype-directed strategy for those with severe asthma.

There are currently 3 monoclonal antibodies approved for children and adolescents. Omalizumab is a monoclonal antibody to IgE, is approved for children and adolescents ≥ 6 years old with allergic sensitization, and has the longest track record for efficacy and safety in children with multiple clinical trials and real-world use studies showing reduced exacerbations and hospitalizations, improved lung function, a steroid-sparing effect, and fewer adverse events than placebo other than injection site reactions.^{53,68} Omalizumab also reduces the fall exacerbation phenomenon in allergic children with asthma, with evidence for specific effects against rhinovirus infection.^{18,69,70} Although studies of omalizumab have included those with moderate and severe asthma, the cost and burden of treatment (injections given every 2–4 weeks under medical supervision due to concerns about anaphylaxis) has generally limited its use to those with more severe disease.

Another class of biologics includes mepolizumab and benralizumab, which target either interleukin (IL)-5 ligand or receptor, respectively, are recommended as an adjunct in those with persistent eosinophilic inflammation. Mepolizumab is a monoclonal antibody against IL-5, which disrupts eosinophil maturation resulting in reduction of eosinophils in sputum and blood. It is currently approved for children ≥ 12 years old with blood eosinophils ≥ 150 cells per μL , and is dosed every 4 weeks. Several studies have demonstrated that mepolizumab significantly reduces the number of asthma exacerbations⁷¹ and has significant glucocorticoid-sparing effects in patients with severe eosinophilic asthma compared with placebo.⁷² In addition, another study demonstrated that treatment with either intravenous or subcutaneous doses was effective at reducing exacerbations and improving quality of life.⁷³

Similarly, benralizumab is an anti-eosinophilic monoclonal antibody; however, its target is IL-5 receptor α . In contrast to other therapies that target IL-5 directly and only reduce eosinophils, benralizumab targets the receptor, thus resulting in rapid eosinophilic depletion.⁷⁴ It is currently approved for children ≥ 12 years old with severe or uncontrolled asthma with eosinophilia. Clinical trials have demonstrated that benralizumab was well tolerated, as seen by low discontinuation rate and had few drug-related adverse events.⁷⁵ Additional potential advantages of benralizumab include its direct action to deplete blood eosinophils compared with the indirect action of those medicines that target the IL-5 ligand (mepolizumab and reslizumab), as well as every 8-week dosing interval to help lower disease burden and health care costs compared with other biologics.⁷⁴ Findings from 2 studies showed benralizumab resulted in substantial improvements in asthma exacerbations, lung function, and symptom control when used as add-on therapy for patients with severe, uncontrolled asthma with elevated baseline blood eosinophils.

Dupilumab, an monoclonal antibody to the alpha subunit of the IL-4 receptor, resulting in reduction in IL-4 and IL-13, is currently under review at the Food and Drug Administration for the treatment of moderate to severe asthma in patients ≥ 12 years old based on clinical trials showing steroid-sparing effects,⁷⁶ reduced exacerbations, and improved lung function.⁷⁷ Data in adolescents for mepolizumab, benralizumab, and dupilumab are quite limited, with a small number of adolescents included in the major clinical trials for each.

PROGNOSIS

The goals of treatment of severe childhood asthma include symptom and exacerbation management, but as pediatricians we are also concerned with prevention of progression of asthma into adulthood. Cross-sectional data and data from the longitudinal SARP III cohort suggest that many children with severe asthma experience at least a transient improvement in asthma severity during adolescence and early adulthood.^{78–80} However, this improvement does not include lung function deficits, and children with a range of asthma severity and treatment may develop irreversible obstruction or chronic obstructive pulmonary disease (COPD).^{81,82} In a landmark longitudinal analysis of children with mild to moderate asthma enrolled in the CAMP study, only 25% had normal lung function patterns in early adulthood, with the remaining participants showing either reduced growth, early decline, or both.⁸¹ More than 1 in 10 met criteria for COPD in their early 20s. Impaired lung function at enrollment and male sex were the strongest predictors for abnormal lung function in early adulthood. These findings suggest that even mild to moderate asthma in early life impacts lifelong health.⁸¹ Although the longitudinal analysis of lung function in the CAMP study included only those with mild-to-moderate asthma, some studies have shown the risk for COPD is higher in children with more severe disease.^{83,84} Data from the SARP suggests irreversible obstruction is less common in children than in adults,⁸⁵ and additional study of effective strategies to prevent lung function decline is an important area of unmet need.⁸⁶

ADVOCACY

Severe asthma is tightly linked with socioeconomic status and minority race and ethnicity in the United States. Markers of asthma severity, including emergency room use, hospitalizations, and deaths due to asthma are all substantially higher in poor and minority populations than their more affluent white peers.^{87,88} Implementation of guidelines-based care with good adherence to standard therapies results in improved asthma control even in high-risk populations,⁸⁹ although high rates of difficult-to-control asthma may persist even in the setting of a clinical trial.⁹⁰ The underlying causes of asthma disparities are complex,²⁵ but include environmental exposures at home and in schools (allergens, indoor and outdoor air pollution),⁹¹ neighborhood level factors,⁹² access to care and treatment,^{93,94} caretaker stress and mental health,⁹⁵ and financial and social hardships.⁹⁶ Although interventions that address the social determinants of health relevant to asthma reduce morbidity,^{97–100} sustaining these programs outside the context of clinical research is challenging and requires health care providers and institutions to form partnerships with legal professionals, community-based programs, insurance programs, and legislators.^{101–104} Given the high cost of biological therapies for asthma, we suggest these types of collaborations and advocacy on behalf of our patients with severe asthma are a component of personalized medicine that should not be overlooked.

SUMMARY

Children with severe asthma require a detailed medical workup, careful consideration of alternative diagnoses, assessment of adherence to medications and self-management plans, and evaluation of comorbid conditions. This multidisciplinary approach is critical to optimize care in this high-risk severe asthma population. Further research and validation of phenotype/endotype clusters in more longitudinal studies are an important next step. These efforts are essential to develop frameworks to

classify severe asthma, personalize therapy, and develop new strategies that address unmet needs. The role of social determinants of health and advocacy for health policies that address modifiable factors is a critical part of the care of children with severe asthma.

REFERENCES

1. Lemanske RF, Busse WW. Asthma: clinical expression and molecular mechanisms. *J Allergy Clin Immunol* 2010;125(2):S95–102.
2. Centers for Disease Control and Prevention. CDC - asthma - Table 4-1 current asthma prevalence percents by age. Atlanta (GA): NHIS; 2015. Available at: <https://www.cdc.gov/asthma/nhis/2015/table4-1.htm>. Accessed May 5, 2018.
3. Childhood Asthma Management Program Research Group, Szeffler S, Weiss S, Tonascia J, et al. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054–63.
4. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43(2):343–73.
5. Fitzpatrick AM, Gaston BM, Erzurum SC, et al. National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. Features of severe asthma in school-age children: atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol* 2006;118(6):1218–25.
6. Haselkorn T, Fish JE, Zeiger RS, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2009;124(5):895–902.e1-4.
7. Bossley CJ, Saglani S, Kavanagh C, et al. Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. *Eur Respir J* 2009;34(5): 1052–9.
8. Bush A, Fleming L, Saglani S. Severe asthma in children. *Respirology* 2017; 22(5):886–97.
9. Jochmann A, Artusio L, Jamalzadeh A, et al. Electronic monitoring of adherence to inhaled corticosteroids: an essential tool in identifying severe asthma in children. *Eur Respir J* 2017;50(6):1700910.
10. Stingone JA, Claudio L. Disparities in the use of urgent health care services among asthmatic children. *Ann Allergy Asthma Immunol* 2006;97(2):244–50.
11. Alvarez G, Schulzer M, Jung D, et al. A systematic review of risk factors associated with near-fatal and fatal asthma. *Can Respir J* 2005;12(5):265–70.
12. Haselkorn T, Zeiger RS, Chipps BE, et al. Recent asthma exacerbations predict future exacerbations in children with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2009;124(5):921–7.
13. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med* 2017;195(3):302–13.
14. Teague WG, Phillips BR, Fahy JV, et al. Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract* 2018;6(2):545–54.e4.
15. Heymann PW, Carper HT, Murphy DD, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. *J Allergy Clin Immunol* 2004;114(2):239–47.

16. Simpson A, Tan VYF, Winn J, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010;181(11):1200–6.
17. Fitzpatrick AM, Teague WG. Severe asthma in children: insights from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *Pediatr Allergy Immunol Pulmonol* 2010;23(2):131–8.
18. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (Anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364(11):1005–15.
19. Yunginger JW, Reed CE, O'Connell EJ, et al. A community-based study of the epidemiology of asthma: incidence rates, 1964–1983. *Am Rev Respir Dis* 1992;146(4):888–94.
20. Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. *PLoS One* 2010;5(4):e10134. Stanojevic S, ed.
21. Jaakkola J, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2006;118(4):823–30.
22. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. *BMC Pediatr* 2013;13(1):121.
23. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. *Curr Opin Allergy Clin Immunol* 2009;9(2):154–60. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19326508>. Accessed May 29, 2018.
24. Gupta RS, Zhang X, Sharp LK, et al. Geographic variability in childhood asthma prevalence in Chicago. *J Allergy Clin Immunol* 2008;121(3):639–45.e1.
25. Wright RJ, Subramanian SV. Advancing a multilevel framework for epidemiologic research on asthma disparities. *Chest* 2007;132(5 Suppl):757S–69S.
26. Fitzpatrick AM, Teague WG, Meyers DA, 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(2):382–9.e1-13.
27. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. *Pediatrics* 2009;123(Supplement 3):S174–84.
28. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005;26(1):89–113.
29. Federico MJ, Liu AH. Overcoming childhood asthma disparities of the inner-city poor. *Pediatr Clin North Am* 2003;50(3):655–75, vii. <http://www.ncbi.nlm.nih.gov/pubmed/12877240>. Accessed May 29, 2018.
30. Leong AB, Ramsey CD, Celedón JC. The challenge of asthma in minority populations. *Clin Rev Allergy Immunol* 2012;43(1–2):156–83.
31. Busse WW, Mitchell H. Addressing issues of asthma in inner-city children. *J Allergy Clin Immunol* 2007;119(1):43–9.
32. Wright RJ. Perinatal stress and early life programming of lung structure and function. *Biol Psychol* 2010;84(1):46–56.
33. van de Loo KFE, van Gelder MMHJ, Roukema J, et al. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur Respir J* 2016;47(1):133–46.
34. Hartwig IRV, Sly PD, Schmidt LA, et al. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. *J Allergy Clin Immunol* 2014;134(1):160–9.
35. Thorburn AN, McKenzie CI, Shen S, et al. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat Commun* 2015;6(1):7320.

36. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010;181(4):315–23.
37. O'Toole J, Mikulic L, Kaminsky DA. Epidemiology and pulmonary physiology of severe asthma. *Immunol Allergy Clin North Am* 2016;36(3):425–38.
38. Mauad T, Silva LFF, Santos MA, et al. Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. *Am J Respir Crit Care Med* 2004;170(8):857–62.
39. Payne DNR, Rogers AV, Adelroth E, et al. Early thickening of the reticular basement membrane in children with difficult asthma. *Am J Respir Crit Care Med* 2003;167(1):78–82.
40. Tillie-Leblond I, de Blic J, Jaubert F, et al. Airway remodeling is correlated with obstruction in children with severe asthma. *Allergy* 2008;63(5):533–41.
41. Dolhnikoff M, da Silva LFF, de Araujo BB, et al. The outer wall of small airways is a major site of remodeling in fatal asthma. *J Allergy Clin Immunol* 2009;123(5):1090–7, 1097.e1.
42. Gibson PG, Norzila MZ, Fakes K, et al. Pattern of airway inflammation and its determinants in children with acute severe asthma. *Pediatr Pulmonol* 1999;28(4):261–70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10497375>. Accessed May 4, 2018.
43. Andersson CK, Adams A, Nagakumar P, et al. Intraepithelial neutrophils in pediatric severe asthma are associated with better lung function. *J Allergy Clin Immunol* 2017;139(6):1819–29.e11.
44. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178(7):667–72.
45. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160(3):1001–8.
46. Brown SD, Brown LA, Stephenson S, et al. Characterization of a high TNF- α phenotype in children with moderate-to-severe asthma. *J Allergy Clin Immunol* 2015;135(6):1651–4.
47. O'Brien CE, Tsirilakis K, Santiago MT, et al. Heterogeneity of lower airway inflammation in children with severe-persistent asthma. *Pediatr Pulmonol* 2015;50(12):1200–4.
48. Bossley CJ, Fleming L, Gupta A, et al. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. *J Allergy Clin Immunol* 2012;129(4):974–82.e13.
49. Hansbro PM, Starkey MR, Mattes J, et al. Pulmonary immunity during respiratory infections in early life and the development of severe asthma. *Ann Am Thorac Soc* 2014;11(Supplement 5):S297–302.
50. Hilty M, Burke C, Pedro H, et al. Disordered microbial communities in asthmatic airways. *PLoS One* 2010;5(1):e8578. Neyrolles O, ed.
51. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol* 2017;140(4):895–906.
52. Bacharier LB, Strunk RC, Mauger D, et al. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;170(4):426–32.
53. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014;(1):CD003559.

54. (* NEW) 2018 GINA Report: global strategy for asthma management and prevention | Global Initiative for Asthma – GINA. Available at: <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed May 1, 2018.
55. Chang TS, Lemanske RF, Mauger DT, et al. Childhood asthma clusters and response to therapy in clinical trials. *J Allergy Clin Immunol* 2014;133(2):363–9.
56. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012;18(5):716–25.
57. Reddel H. Emerging concepts in evidence-based asthma management. *Semin Respir Crit Care Med* 2018;39(01):82–90.
58. Robinson DS, Campbell DA, Durham SR, et al. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003;22(3):478–83.
59. Barsky EE, Giancola LM, Baxi SN, et al. A practical approach to severe asthma in children. *Ann Am Thorac Soc* 2018;15(4):399–408.
60. Tantisira KG, Fuhlbrigge AL, Tonascia J, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. *J Allergy Clin Immunol* 2006;117(6):1264–71.
61. Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society Statement: pulmonary function testing in pre-school children. *Am J Respir Crit Care Med* 2007;175(12):1304–45.
62. Busse WW, Camargo CA, Boushey HA, et al. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma - Summary Report 2007. Washington, DC: US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2007.
63. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31(1):143–78.
64. Chung KF. Diagnosis and management of severe asthma. *Semin Respir Crit Care Med* 2018;39(01):091–9.
65. Guidelines for the diagnosis and management of asthma (EPR-3) | National Heart, Lung, and Blood Institute (NHLBI). Available at: <https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma>. Accessed May 20, 2018.
66. Bossley CJ, Fleming L, Ullmann N, et al. Assessment of corticosteroid response in pediatric patients with severe asthma by using a multidomain approach. *J Allergy Clin Immunol* 2016;138(2):413–20.e6.
67. Rodrigo GJ, Neffen H. Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: a systematic review. *Pediatr Allergy Immunol* 2017;28(6):573–8.
68. Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc* 2017;38(4):250–63.
69. Esquivel A, Busse WW, Calatroni A, et al. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. *Am J Respir Crit Care Med* 2017;196(8):985–92.
70. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136(6):1476–85.
71. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380(9842):651–9.

72. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371(13):1189–97.
73. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371(13):1198–207.
74. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α 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(10056):2128–41.
75. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;388(10056):2115–27.
76. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018. <https://doi.org/10.1056/NEJMoa1804093>.
77. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018. <https://doi.org/10.1056/NEJMoa1804092>.
78. Centers for Disease Control and Prevention. National Center for Environmental Health, Division of Environmental Hazards and Health Effects, Centers for Disease Control and Prevention, Asthma Surveillance Data. Available at: <https://www.cdc.gov/asthma/asthmadata.htm>. Accessed 2016.
79. Zein JG, Udeh BL, Teague WG, et al. Impact of age and sex on outcomes and hospital cost of acute asthma in the United States, 2011–2012. *PLoS One* 2016; 11(6). <https://doi.org/10.1371/journal.pone.0157301>.
80. Gupta R, Margevicius S, DeBoer M, et al. Children with severe asthma are likely to become less severe during adolescence: preliminary results of the SARP III pediatric longitudinal study. *Am Thorac Soc Int Meet* 2018;A7806. Available at: https://www.atsjournals.org/doi/abs/10.1164/ajrccmconference.2018.197.1_MeetingAbstracts.A7806.
81. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374(19):1842–52.
82. Vonk JM, Jongepier H, Panhuysen CIM, et al. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003;58(4):322–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12668795>. Accessed May 5, 2018.
83. Tai A, Tran H, Roberts M, et al. Outcomes of childhood asthma to the age of 50 years. *J Allergy Clin Immunol* 2014;133(6):1572–8.e3.
84. Tai A, Tran H, Roberts M, et al. The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014;69(9):805–10.
85. Phipatanakul W, Mauger DT, Sorkness RL, et al. Effects of age and disease severity on systemic corticosteroid responses in asthma. *Am J Respir Crit Care Med* 2017;195(11):1439–48.
86. Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018. [https://doi.org/10.1016/S2213-2600\(18\)30100-0](https://doi.org/10.1016/S2213-2600(18)30100-0).
87. Akinbami LJ, Moorman JE, Garbe PL, et al. Status of childhood asthma in the United States, 1980–2007. *Pediatrics* 2009;123(Supplement 3):S131–45.

88. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. *Pediatrics* 2002;110(2 Pt 1):315–22.
89. Gruchalla RS, Sampson HA, Matsui E, et al. Asthma morbidity among inner-city adolescents receiving guidelines-based therapy: role of predictors in the setting of high adherence. *J Allergy Clin Immunol* 2009;124(2):213–21.e1.
90. Pongracic JA, Krouse RZ, Babineau DC, et al. Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents. *J Allergy Clin Immunol* 2016;138(4):1030–41.
91. Liu AH, Babineau DC, Krouse RZ, et al. Pathways through which asthma risk factors contribute to asthma severity in inner-city children. *J Allergy Clin Immunol* 2016;138(4):1042–50.
92. Beck AF, Simmons JM, Huang B, et al. Geomedicine: area-based socioeconomic measures for assessing risk of hospital reutilization among children admitted for asthma. *Am J Public Health* 2012;102(12):2308–14.
93. Price JH, Khubchandani J, McKinney M, et al. Racial/ethnic disparities in chronic diseases of youths and access to health care in the United States. *Bio-med Res Int* 2013;2013:1–12.
94. Kattan M, Mitchell H, Eggleston P, et al. Characteristics of inner-city children with asthma: the National Cooperative Inner-City Asthma Study. *Pediatr Pulmonol* 1997;24(4):253–62.
95. Rosa MJ, Lee AG, Wright RJ. Evidence establishing a link between prenatal and early-life stress and asthma development. *Curr Opin Allergy Clin Immunol* 2018;18(2):1.
96. Beck AF, Huang B, Simmons JM, et al. Role of financial and social hardships in asthma racial disparities. *Pediatrics* 2014;133(3):431–9.
97. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351(11):1068–80.
98. Leas BF, D'Anci KE, Apter AJ, et al. Effectiveness of indoor allergen reduction in asthma management: A systematic review. *J Allergy Clin Immunol* 2018;141(5):1854–69.
99. Permaul P, Phipatanakul W. School environmental intervention programs. *J Allergy Clin Immunol Pract* 2018;6(1):22–9.
100. Al Alooia NA, Naik-Panvelkar P, Nissen L, et al. Asthma interventions in primary schools—a review. *J Asthma* 2014;51(8):779–98.
101. Carpenter LM, Lachance L, Wilkin M, et al. Sustaining school-based asthma interventions through policy and practice change. *J Sch Health* 2013;83(12):859–66.
102. Beck AF, Klein MD, Schaffzin JK, et al. Identifying and treating a substandard housing cluster using a medical-legal partnership. *Pediatrics* 2012;130(5):831–8.
103. Klein MD, Beck AF, Henize AW, et al. Doctors and lawyers collaborating to HeLP Children—: outcomes from a successful partnership between professions. *J Health Care Poor Underserved* 2013;24(3):1063–73.
104. Raphael JL, Colvin JD. More than wheezing: incorporating social determinants into public policy to improve asthma outcomes in children. *Pediatr Res* 2017;81(1):2–3.