Overview of severe asthma, with emphasis on pediatric patients: a review for practitioners

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ABSTRACT

Asthma is the most common life-threatening chronic disease in children. Although guidelines exist for the diagnosis and treatment of asthma, treatment of severe, pediatric asthma remains difficult. Limited studies in the pediatric population on new asthma therapies, complex issues with adolescence and adherence, health disparities, and unequal access to guideline-based care complicate the care of children with severe, persistent asthma. The purpose of this review is to provide an overview of asthma, including asthma subtypes, comorbidities, and risk factors, to discuss diagnostic considerations and pitfalls and existing treatments, and then present existing and emerging therapeutic approaches to asthma management. An improved understanding of asthma heterogeneity, clinical characteristics, inflammatory patterns, and pathobiology can help further guide the management of severe asthma in children. More studies are needed in the pediatric population to understand emerging therapeutics application in children. Effective multimodal strategies tailored to individual characteristics and a commitment to address risk factors, modifiers, and health disparities may help reduce the burden of asthma in the USA.

BACKGROUND

Over six million children are affected by asthma in the USA, making asthma one of the most common chronic conditions among children.[1] The burden of asthma is high and not uniformly distributed; children from minority groups and/or with low resources are disproportionately affected by asthma morbidity and mortality.[2]

Asthma is not a single disease; it is characterized by variable disease expression, severity, and pathobiology.[3] It is a complex, heterogeneous, inflammatory disorder with diverse physiological characteristics and molecular mechanisms.[4] Asthma affects the small and large airways and is characterized by variable airflow obstruction, bronchial hyper-responsiveness, inflammation, hyperinflation, and air trapping.[4] There are distinct phenotypes linked to age, gender, and genetic background, which may vary from those seen in adults.[5] Various psychosocial influences and gene-by-environment interactions may help explain the heterogeneity and variability of asthma phenotypes.[6 7] It is believed that epigenetic changes such as DNA methylation and histone modifications play a role in the development and maintenance of asthma by modulating gene expression.[7] Hence asthma morbidity combines genetic predisposition and environmental factors that complicate evaluation and treatment in severe, persistent asthma.

Managing children with severe asthma is similar to, but not the same as, adults. Often, treatment options include extrapolating data from adult studies to help guide management. Limited studies in the pediatric population on new asthma therapies, complex issues with adolescence and adherence, health disparities, and unequal access to guideline-based treatment complicate the care of a child with severe, uncontrolled asthma. Asthma subspecialists have been shown to improve asthma outcomes and be more consistent with treatment guidelines; however, many children do not have adequate access to subspecialty services.[8–10] Community pediatricians are often the main providers caring for children with severe asthma and need specific guidance on new and emerging therapeutic options.[10–12] Studies have shown that access to guideline-based asthma care in the community, especially in urban areas with low-income minority families, is limited and challenging, making the dissemination of knowledge imperative.

The purpose of this review is to provide an overview of asthma, including asthma subtypes, comorbidities, and risk factors, to discuss diagnostic considerations and pitfalls and existing treatments, and then present existing and emerging therapeutic approaches to asthma management.

ASTHMA SUBTYPES

Several classifications of asthma have been introduced and proposed over the years. Recently, there has been a movement toward phenotyping and endotyping asthma to potentially improve therapeutic interventions and allow for more individualized therapies. Phenotyping and endotyping can be particularly valuable in severe, persistent, difficult-to-control asthma. Asthma phenotypes include observable clinical characteristics of disease seen in patients.[13] Endotypes describe the underlying pathophysiological or molecular processes driving these phenotypes.[14]

Clinical phenotypes

Allergic asthma and non-allergic asthma

Traditionally, asthma is classified as *allergic* or *non-allergic*. *Allergic asthma* is considered a form of IgE-mediated hypersensitivity (Gell and Coombs type I) and is usually precipitated by exposure to aeroallergens.[15] Elevated antigen-specific IgE antibodies found by skin prick test typically indicate allergic sensitization.[16] Allergic asthma is predominantly early onset,[17] and approximately 80%–90% of children with asthma have allergies.[18] Allergic asthma is one of the clinical manifestations of atopy and part of the atopic march, with 60%–70% of cases with severe atopic dermatitis developing asthma.[19 20] A weakened and dysfunctional skin barrier is thought to provoke the atopic march and facilitate allergic sensitization.[19] In *non-allergic asthma*, allergic sensitization and atopy are not observed, it is later in onset, and may not be as responsive to standard therapies.[21]

Childhood wheezing and early-life exposures

Early life may highlight risk factors and display phenotypic characteristics involved in the development of asthma in children.[22] Host susceptibility, allergic sensitization, parental atopy, and viral-induced wheezing are thought to influence asthma development in children.[23] Preschoolers may get exposed to viruses that trigger asthma-like symptoms.[24] These infections may lead to future asthma development in a subset of children who wheeze.[24]

Wheezing phenotypes that implicate asthma have been investigated in young children. In some cases, children may continue to have recurrent wheezing episodes into late childhood. A pooled analysis of five birth cohorts identified five main wheeze phenotypes based on age of onset and the frequency and persistence of wheezing episodes.[25] According to the analysis, children who wheezed showed reduced lung function, and the greatest association with asthma was seen in children with persistent wheezing.[25]

Respiratory syncytial virus (RSV) and rhinovirus (RV) are two viruses linked to early childhood wheezing illnesses and implicated in asthma pathogenesis.[26] In the childhood origins of asthma (COAST) cohort, early childhood RV/RSV wheezing illnesses increased the risk of asthma by age 6.[25] Additionally, RV infection during the first 3 years of life was associated with subsequent development of asthma.[27] Severe RSV bronchiolitis in infancy requiring hospitalization increased the risk of developing asthma.[28] However, it is still unclear if RV and RSV respiratory illnesses actually cause asthma or unmask risks for asthma development. The use of asthma predictive indices helps predict future asthma development.[29] The modified Asthma Predictive Index and the University of Cincinnati Asthma Predictive Index consider risk factors including parental and personal atopy and other markers to predict risk of future asthma development.[29]

Lung trajectories

Asthma control in childhood may predict disease severity in adulthood. Bui and colleagues[30] found that lung function impairment in childhood increased the risk of developing future chronic obstructive lung disease. Atopy and early-life exposures to smoking and lung infections, exacerbated by factors in adulthood, were related to this risk. Early control of risk factors may prevent further progression of disease in adulthood.[30] Six lung function trajectories were identified: (1) *average* (lung function); (2) *persistently high*; (3) *early below average* (lung function or forced expiratory volume in 1 s (FEV_1)) in childhood, (followed by) *accelerated decline* in adulthood; (4) *below average* (FEV_1); (5) *persistently low* (FEV_1); and (6) *early low* (lung function) in childhood, (followed by) *accelerated growth* (improvement phase), then *normal* (average) *decline* in adulthood.

Clustering in asthma

Clinical phenotypes can further be distinguished by cluster analysis to reveal patterns. Much of the available data are in adults and have identified clinical clusters with overlap such as early-onset, atopic asthma, and later-onset, non-atopic, non-eosinophilic asthma in obese female subjects (table 1).[31–33] Fitzpatrick and colleagues[34] investigated severe asthma heterogeneity in a diverse sample of 161 children aged 6–17 years enrolled in the Severe Asthma Research Program. They identified four clusters based on age of onset and duration of asthma, phenotypic characterization, lung volume, comorbidities, medication use, and healthcare utilization.[34] Cluster 1 was classified as late-onset symptomatic asthma with normal lung function, cluster 2 as early-onset atopic asthma with normal lung function, cluster 3 as early-onset atopic asthma with mild airflow limitation, and cluster 4 as early-onset atopic asthma with advanced airflow limitation.[34] Additional studies may help further characterize phenotypic clusters in children.

Asthma-related obesity

Obesity is a risk factor for asthma and is common.[35] Obesity may alter lung function both mechanically and biologically.[35] Obesity-mediated inflammation, metabolic dysregulation, and epigenetic changes may play a role in poor asthma control and decrease response to controller medications.[35] The National Health and Nutrition Examination Survey data found obesity in children strongly associated with non-allergic asthma versus atopic asthma.[36]

Cellular, molecular, and inflammatory phenotypes

Another way to phenotype asthma is based on inflammatory characteristics. Blood and sputum analysis/bronchioalveolar lavage (BAL) help, but are not routinely obtained, especially in children.[37] Four inflammatory phenotypes were identified based on cellular profiles of induced sputum: *eosinophilic*, *neutrophilic*, *paucigranulocytic* and *mixed neutrophilic-eosinophilic* (also called *mixed granulocytic*).[38] Wang *et al*[37] found >3% sputum eosinophils in eosinophilic asthma and >61% sputum neutrophils in neutrophilic asthma.

Eosinophilic and non-eosinophilic asthma

Eosinophilic asthma is typically associated with atopy, allergic sensitization, and eosinophilia.[39] It is often seen in childhood, and the degree of eosinophilic inflammation usually correlates with asthma severity.[40] Eosinophilic asthma generally responds well to inhaled corticosteroids (ICS), steroids, anti-IgE or antieosinophilic therapies.[39] *Non-eosinophilic asthma* is associated with obesity, smoking, microbial respiratory colonization/infection, pollutants,

Table 1 Cluster analysis and some clinical asthma phenotypes in adults

Phenotypic classification by Haldar et al and Hirose and Hiroguchi[31 33]	Phenotypic classification by Moore et al and Hirose and Hiroguchi[32 33]
Benign asthma ▶ Mild disease. ▶ Mild symptoms. ▶ Minimal airway inflammation. ▶ Rare exacerbations.	*Mild atopic asthma, early onset* ▶ Young, active individuals. ▶ Normal lung function. ▶ Infrequent exacerbations. ▶ Activity and exercise-related symptoms are common.
Early-onset, atopic asthma ▶ Associated with atopy. ▶ Presents at an early age. ▶ Eosinophilic airway inflammation. ▶ High risk of morbidity. ▶ Increased healthcare utilization. ▶ Treatment should target atopic/ eosinophilic inflammation.	*Moderate atopic asthma, early onset* ▶ Associated with atopy. ▶ Presents at an early age. ▶ Preserved lung function. ▶ Increased healthcare utilization. ▶ ≥3 controllers may be needed to control symptoms.
Obese, non-eosinophilic asthma ▶ Seen in obese female subjects. ▶ Late-onset presentation. ▶ Decreased atopy. ▶ Moderate airway hyper-reactivity and FEV_1 reversibility. ▶ High healthcare utilization. ▶ Minimal eosinophilic airway inflammation. ▶ Symptom control with high-dose ICS + other controllers*. ▶ Weight loss highly recommended.	*Non-atopic asthma, late onset* ▶ Seen in obese women. ▶ Moderate decline in FEV_1. ▶ High healthcare utilization. ▶ Minimal eosinophilic airway inflammation. ▶ Symptom control with high-dose ICS + other controllers*.
Early-onset, symptom-predominant asthma ▶ Minimal airway reversibility. ▶ Minimal eosinophilic inflammation. ▶ Requires multiple controller medications*. ▶ Challenging to treat. ▶ Usually severe, persistent.	*Severe atopic asthma with reversible airflow, early onset* ▶ Associated with atopy. ▶ Severe airway obstruction with FEV_1 reversibility. ▶ High healthcare utilization, with ICU admission. ▶ Requires high-dose ICS + other controllers*. ▶ Associated with poor quality of life.
Late-onset, inflammation-predominant asthma ▶ Male predominant. ▶ Significant eosinophilic disease is present. ▶ Treatment should target eosinophilic inflammation. ▶ Challenging to treat. ▶ Usually severe, persistent.	*Severe 'non-atopic' asthma with fixed airflow, late onset* ▶ Infrequently associated with atopy. ▶ Severe airway obstruction. ▶ High healthcare utilization, with ICU admission. ▶ Challenging to treat, OCS + other controllers*. ▶ Associated with poor quality of life.

*Controllers/controller medications include ICS, LABA, LTRA, and LAMA. FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; ICU, intensive care unit; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids.

and less with atopy.[41] Non-eosinophilic asthma may lead to difficult-to-treat, persistent asthma.[41]

Blood eosinophils
In children, cellular phenotypes are identified mainly by blood analysis.[42] Children with aeroallergen sensitization plus blood eosinophils of ≥300 cells/µL were more likely to respond to ICS.[42] Blood eosinophil counts are useful biomarkers in severe asthma management,[43 44] but other entities such as vasculitides and malignancy must be ruled out when counts are elevated.[45]

Th2 and non-Th2 pathways and role of IgE
Based on available studies, asthma endotypes can be broadly classified into T helper 2 (Th2) and non-Th2 pathways.[46]

Th2 endotypes are characterized by elevated eosinophil counts in sputum, BAL, and/or blood.[13] Release of interleukin (IL) 4, IL-5, and IL-13 upregulates inflammation when the respiratory epithelium is exposed to irritants.[46 47] Elevated total and antigen-specific IgE are linked to allergic asthma and may be markers of severity.[48 49] Cigarette exposure was also associated with higher IgE levels.[49]

Non-Th2 or non-eosinophilic asthma pathways are not well understood. A subpopulation of T helper cells (Th17) produce IL-17A, IL-17F, and tumor necrosis factor-alpha and are involved in severe non-eosinophilic asthma.[50] IL-17 is associated with neutrophilic inflammation and upregulation of IL-6 and IL-8 by airway epithelial cells in severe asthma.[50] Transforming growth factor-beta, IL-17, and IL-1 appear to be involved in airway remodeling and fibrotic changes.[51]

ESTABLISHING ASTHMA DIAGNOSIS
The first step in evaluating children with asthma is to confirm the diagnosis. It may be challenging to diagnose asthma in early childhood given viral wheezing mimicks asthma symptoms and because objective testing is difficult to obtain in young children.[52] Asthma remains a clinical diagnosis based on thorough history, physical examination, and response to treatment; however, tools provide objective support of asthma. Although other diagnostic modalities exist, we will concentrate on the following objective tools in asthma diagnosis: spirometry, methacholine bronchoprovocation, exercise challenge testing, and fractional exhaled nitric oxide (FeNO).[53]

Spirometry
Spirometry is valuable in diagnosing, monitoring, and managing asthma.[54] Spirometry evaluates the extent of airflow obstruction and degree of reversibility.[54] Postbronchodilator FEV_1 and/or forced vital capacity (FVC) improvement from baseline of at least 12% in children plus exceeding 200 mL in adults represents 'significant' bronchodilation and is an important diagnostic criterion for reversible obstructive airway defects.[55] However normal spirometry does not exclude asthma, and asthma remains a clinical diagnosis. The National Asthma Education and Prevention Program (NAEPP) recommends spirometry to detect airflow obstruction in children ≥5 years.[56] Obtaining reproducible and acceptable flow-volume loops in young children may be difficult.[57] Children may also have an intact FEV_1 and therefore the FEV_1:FVC ratio (<80%) is an important obstruction marker in children.[58] The utility of forced expiratory flow 25–75 is controversial because it lacks specificity and is not reliable.[59] However, it may serve as a surrogate for small airway obstruction in children with ventilatory defects.[60] Full pulmonary function testing which

includes spirometry, lung volumes, and diffusing capacity is helpful when asthma diagnosis is unclear.[61]

Methacholine bronchoprovocation

Methacholine bronchoprovocation can help establish an asthma diagnosis in the setting of normal spirometry.[62] Asthma is diagnosed based on the degree of FEV_1 reduction, or bronchial hyper-responsiveness, at set standards of methacholine administration.[62] Those with and without asthma are expected to have a reduction in FEV_1; however, in those with asthma, the reduction is greater and at lower concentrations of inhaled methacholine.[62] Positive methacholine challenges are generally from asthma, but could represent alternative diagnoses.[63] Methacholine challenges should not be performed in those with abnormal spirometry results consistent with asthma.[64] There are risks associated with this test, including bronchoconstriction, chest tightness, dyspnea, and coughing.[64] Bronchial challenge testing is not routinely performed in small children.[65]

Exercise challenge testing

Exercise challenge testing can be performed in children to help diagnose asthma, exercise-induced bronchospasm, or other exercise-related breathing disorders. A fall in FEV_1 of >12% predicted or peak expiratory flow >15% is considered a positive test.[53] Exercise challenge is not recommended in children with a baseline FEV1:FVC or FEV_1 <70%.[53]

Fractional exhaled nitric oxide

FeNO measures eosinophilic asthma/type 2 inflammation and may be a useful clinical indicator for uncontrolled asthma. FeNO is higher in atopic disease and with persistent exposure to culprit allergens.[66] FeNO can help monitor airway inflammation, predict ICS responsiveness, and assess adherence.[66] According to the American Thoracic Society (ATS), FeNO >35 parts per billion (ppb) in children usually supports a diagnosis of asthma.[66] FeNO <20 ppb in children suggests low eosinophilic inflammation (or adequate treatment).[66] The Global Initiative For Asthma (GINA) recommends FeNO utilization in severe, difficult-to-treat asthma to guide therapy.[67]

DIFFERENTIAL DIAGNOSIS AND COMORBIDITIES

Children being evaluated for asthma should be assessed thoroughly for external, modifiable factors and conditions that mimic or coexist with asthma. This is especially important when asthma control remains elusive, and patients are not responding to standard therapy. Alternative diagnoses and common comorbidities are listed in table 2.[56 68]

Asthma mimickers

Careful attention to ruling out alternative diagnoses is vital as it can have a crucial impact on treatment modalities, disease course, and complications. Recognition of alternative diagnoses other than asthma is vital and should be considered based on clinical signs and symptoms.[69] Diagnostic modalities including imaging studies (CT scans, chest radiography) should be considered if other conditions are suspected and atypical symptoms are noted.[69]

Table 2 Asthma-related differential diagnosis and common comorbidities[56 68]

Differential diagnosis	Comorbidities
Gastroesophageal reflux disease ± microaspirations	Gastroesophageal reflux disease
Allergic rhinitis and sinusitis	Aspiration
Recurrent viral respiratory infections	Chronic rhinosinusitis
Persistent bacterial bronchitis	Atopy
Chronic upper airway cough syndrome	Obesity
Prolonged viral cough	Sleep disorders
Exercise-induced lung obstruction	Dysfunctional breathing
Neurogenic cough	Vocal cord disorders
Lymphadenopathy or tumor	Adenoidal hypertrophy
Foreign body aspiration	Hypersensitivity pneumonitis
Congenital heart disease	Allergic bronchopulmonary aspergillosis
Vascular rings or laryngeal webs	Alpha-1 antitrypsin deficiency
Tracheal or laryngeal disorders	Autoimmune disease (ie, vasculitis, etc)
Other developmental anomalies/ malformations	Immune dysfunction (ie, common variable immunodeficiency, etc)
Vocal cord disorders	Food allergy
Cystic fibrosis	Aspirin exacerbated respiratory disease
Primary ciliary dyskinesia	Mental/mood disorders
Bronchopulmonary dysplasia	Hormonal influences
Bronchiolitis	
Allergic bronchopulmonary aspergillosis	

Asthma comorbidities

Once a diagnosis of asthma is confirmed and other alternative diagnoses ruled out, comorbidities that may influence control and asthma management should also be considered.[69] There are many comorbidities or factors to consider,[56 68] but the main considerations are listed in table 2.

Special considerations

Allergic bronchopulmonary aspergillosis

It is important to exclude allergic bronchopulmonary aspergillosis (ABPA) in severe asthma. ABPA is characterized by a type 1 hypersensitivity immune reaction to *Aspergillus* antigens, commonly found in the environment.[70] ABPA can be seen with asthma or cystic fibrosis and should be suspected in patients with poor asthma control despite adherence to therapy or with sudden worsening disease.[70] The presence of central bronchiectasis on chest imaging is an important diagnostic criterion, but not required.[71] Total IgE and *Aspergillus fumigatus* IgE and precipitins also help with diagnosis.[71] Because mycoses other than *Aspergillus* can be seen, negative *Aspergillus* precipitins studies should not preclude this diagnosis, and sputum studies for other possible mycotic influencers may be considered.[72] Corticosteroids and azoles are used in the treatment of ABPA. Omalizumab is a potential steroid-sparing option, but more studies are needed.[72]

DEFINITION AND DETERMINATION OF SEVERITY AND CONTROL

Severity

Asthma severity is a reflection of disease intensity.[73] According to the NAEPP guidelines severity is more easily

assessed before initiation of long-term control therapy.[56] The 2007 NAEPP guidelines recognize key components to helping determine severity and control; they include frequency of symptoms, use of rescue inhaler/short-acting beta-agonist (SABA), and interference of asthma symptoms with activity.

Control

Asthma control is based on the clinical assessment (symptom frequency, exacerbations, activity limitation) and medications required to achieve symptom control.[67] Regular clinic appointments help evaluate knowledge, technique, adherence, and therapeutic response. Modifiable risk factors, trigger/allergen exposure, rescue inhaler use, and comorbidities should be assessed.[74] Lung function can be evaluated and validated tools such as Asthma Control Test/Childhood Asthma Control Test/Asthma Control Questionnaire can be used.[74] Treatment regimen and goals of therapy are revisited and can be adjusted or 'stepped up'.[75] Mental health disorders influence asthma and should be screened for and treated.[76] Home visits may help with adherence and control.[77] Shared decision making producing a personalized action plan help asthma self-management.[78]

BARRIERS IN THE MANAGEMENT OF SEVERE PEDIATRIC ASTHMA
Asthma health disparities

Most children with asthma respond well to guideline-based medical therapy; however, many do not receive it.[79 80] In the USA, disparities in asthma prevalence, morbidity, and mortality tend to correlate with socioeconomic status and ethnicity.[81] The burden of asthma is disproportionally higher in low-income, under-represented minority communities, especially African Americans, Puerto Ricans, and Native Americans.[82 83] African Americans and Latinx/Puerto Ricans have the highest rates of asthma, emergency department (ED) visits, and hospitalizations in the USA.[82 83]

Genetics/epigenetics and biological factors alone do not explain these health disparities.[82] There are several factors related to healthcare, economic, and social policies that contribute to poor asthma control, prevalence, and outcomes. These factors include poor access to care and subspecialty referrals, lack of guideline-based care, substandard living/school/work conditions, poor health literacy, religious/cultural beliefs, family dynamics, psychosocial factors, and systemic racism.[81–83]

Environmental influences
Home environment

People with asthma residing in neighborhoods with vulnerable infrastructures and housing have higher exposure to indoor and outdoor pollutants, inadequate ventilation, and excess humidity, which are linked to increased asthma exacerbations.[84 85] Common home allergens include dust mites, rodents, mold, cockroaches, and tobacco.[77] Home visits by qualified professionals may help identify and mitigate home triggers.[77]

School environment

Allergens and pollutants are common in schools, where children spend many hours of the day. Schools may have poor ventilation systems and significant dander and mouse allergens.[86–89] Additionally, inner-city schools are often proximal to industries and dense traffic, leading to disproportionate exposure to air pollutants.[90]

Air pollutants

Several studies have established that children with early exposure to traffic-related air pollutants are at increased risk of developing asthma.[91–98] Increased airway hyperactivity and obstruction following exposure to diesel exhaust are well documented. Air pollutants such as ozone, nitrogen dioxide, sulfur dioxide, and particulate matter 2.5 can worsen respiratory symptoms and increase asthma exacerbations.[99] Young children living in low-resource communities with substandard infrastructures are at increased risk.[99]

Environmental tobacco smoke and vaping

Environmental tobacco smoke (ETS) exposure is an important risk factor for asthma development and management. A number of studies found that exposure to ETS was associated with asthma symptoms in children.[100 101] Electronic cigarette use or vaping is another serious public health concern in the USA,[102] given aerosol exposure to volatile organic compounds (VOCs) and multiple other irritants that they emit.[103] Vaping impacts asthma, impairs ciliary function, and may cause progressive respiratory symptoms and vaping-associated lung injury (EVALI, e-cigarette or vaping product use-associated lung injury).[103 104] Smoking cessation can improve lung function and airway inflammation by week 6.[105]

SEVERE PEDIATRIC ASTHMA MANAGEMENT APPROACHES

Currently, much of the available data for managing severe persistent childhood asthma are extrapolated from studies in adults. Advances in our understanding of pathophysiological processes have brought new optimism to the fields of medicine and molecular immunology and have propelled the exploration of new therapeutic strategies.

In April 2019, GINA updated its guidelines and no longer recommends SABA-only therapy for mild asthma in adults and adolescents.[68] ICS/formoterol combination as a reliever is now recommended across the severity spectrum in both adults and adolescents to reduce the risk of serious exacerbation.[68] GINA also recommends tiotropium as an add-on controller option to high-dose ICS/long-acting beta agonist (LABA) before considering biologics.[68] The updated NAEPP guidelines, recently published in the *Journal of Allergy and Clinical Immunology* in December 2020, recommend ICS/formoterol therapy in a single inhaler as both daily controller and reliever therapy in moderate to severe persistent asthma for individuals 4 years and older.[106] For mild persistent asthma, NAEPP favors use of low-dose ICS in individuals 12 years and older, either as daily therapy with as-needed SABA or as-needed therapy along with SABA.[106] Addition of long-acting muscarinic antagonist (LAMA) to ICS/LABA is also recommended in uncontrolled persistent asthma in individuals 12 years and older.[106] As data continue to emerge we expect more consolidated guidance.

Short-acting bronchodilators

SABA relaxes airway smooth muscle. They are used as relief/rescue therapy universally. GINA and NAEPP no

longer recommend use of SABA alone for mild asthma in adolescents and adults.[68 106]

Inhaled corticosteroids

ICS are classic asthma controller medications that have been well known to reduce airway inflammation and achieve asthma control in most, but not all, children with asthma. ICS dosing can be escalated with increasing severity of symptoms. Prolonged use of medium-dose to high-dose ICS has been associated with adrenal suppression in children, height loss, and possible bone density loss over time, and these adverse effects should be monitored longitudinally.[107 108] Maintenance at the lowest possible dose is encouraged.[108]

Long-acting bronchodilators

LABAs are a common and effective add-on to ICS in the treatment of asthma. ICS/LABA has generally been found superior to antileukotriene (leukotriene receptor antagonist, LTRA) use with ICS in controlling asthma symptoms, improving lung function, and decreasing SABA and systemic steroids use.[109–111] The safety of LABA in asthma especially when used as monotherapy has been a point of controversy. ICS/LABA combinations are safe, but there was concern over past reports of significant risk of exacerbations and asthma-related death associated with LABA monotherapy.[112 113] As trials did not find an increase in serious asthma-related adverse events in adults and children, the Food and Drug Administration (FDA) removed the black box warning for increased risk of death in December 2017.[114 115] LABA should always be used with an ICS in asthma treatment. Use of ICS/LABA once daily over use of ICS/LABA two times per day may improve adherence.[116]

Several meta-analyses of decades of research support the use of ICS/formoterol as a rescue medication, or a combination of rescue and controller medication, known as single maintenance and reliever therapy (SMART), in asthma treatment.[117–119] In a recent landmark study by Beasley et al,[120] it is also becoming clear that ICS/LABA use as needed (specifically budesonide/formoterol) in mild persistent asthma may be as effective and reduce cumulative corticosteroid exposure over time. How we can feasibly implement this in the USA given pharmaceutical and insurance barriers remains to be seen.

Cromolyn

Cromolyn, a mast cell stabilizer, is sometimes used in children with mild asthma and functions by reducing inflammation and bronchospasm.[121] However, ICS is superior.[122 123] Cromolyn has minimal side effects and decreases steroid exposure,[121] but its use is limited by frequent dosing. Cromolyn may be used as an adjunct therapy to ICS for pregnant adolescents.[124]

Methylxanthines

Theophylline is known for its anti-inflammatory and bronchodilator effects and may also improve corticosteroid insensitivity.[125] At higher doses theophylline is associated with side effects including seizures and cardiac arrhythmias. Theophylline interacts with many drugs, increasing its toxicity.[125] We do not routinely recommend use in children.

Long-acting muscarinic antagonists

LAMAs are an ICS add-on therapy that promotes smooth muscle relaxation and decrease bronchial tone.[126] Tiotropium bromide in patients with moderate to severe, persistent asthma—already on medium-dose to high-dose ICS—has been approved in children >6 years and has been shown to improve lung function and reduce exacerbations.[127] It can be used with ICS in patients who cannot tolerate the sides effects of LABA,[128] and are a good option to add for those who are not adequately controlled on ICS/LABA or high-dose ICS therapies, and prior to moving to biologics or other immunomodulators.[68]

Leukotriene receptor antagonists

LTRAs have anti-inflammatory effects and may be used as monotherapy or an add-on therapy with ICS in persistent asthma.[129] LTRAs are also used in other atopic disorders. In persistent asthma, LTRA+ICS does not appear to be as effective as LABA/ICS.[130] ICS monotherapy is superior to LTRAs,[129] but LTRAs are a good option for mild asthma in families who are concerned or in children who cannot tolerate ICS.[131] They are not appropriate for monotherapy in severe asthma. In March 2020, the FDA added a boxed warning about neuropsychiatric risks associated with montelukast use, which should be discussed with patients/caregivers prior to starting.[132] However, overall LTRAs have a good safety profile.

Systemic corticosteroids

Patients with severe uncontrolled asthma may require systemic corticosteroids to achieve control and may have corticosteroid insensitivity.[133] Maintenance oral corticosteroids should be avoided as much as possible due to well-known adverse effects associated with prolonged use. Steroid-sparing options should be considered in the management of severe, uncontrolled asthma in every case.[68] If chronic steroids are required, every effort to reduce to the minimal controlling dosage and screening for steroid effects (ie, blood pressure, eye pressure, height/weight, adrenal axis, bone densitometry, etc) should be employed.[134]

Triple therapy

In the USA, single-inhaler triple therapy is not yet FDA-approved for asthma in children. Based on its effectiveness in chronic obstructive pulmonary disease,[135] triple therapy was investigated in the treatment of asthma in adults. Adult trials with single-inhaler triple therapy (ICS/LABA/LAMA) showed improvement in lung function and exacerbations in severe asthma in Europe.[136] Further studies in children are needed, but this can be a lucrative option in children with severe asthma and may help facilitate adherence.

Antimicrobials

The 2019 GINA guidelines recommend off-label use of low-dose azithromycin for acute management of symptomatic patients with asthma who are already on moderate-dose to high-dose ICS/LABA.[68] According to the Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES) trial, low-dose azithromycin has both anti-infective and anti-inflammatory properties that can reduce asthma

exacerbations and improve quality of life in adults.[137] Use of antimicrobials in the treatment of children with severe asthma is still being investigated and is not routinely recommended at this time. However, it has been suggested that azithromycin could help children with severe, neutrophilic asthma.[138]

Allergen immunotherapy

Allergen immunotherapy (AIT) has been used for decades and continues to evolve. It is an effective treatment for asthma.[139] It can modify the course of disease and help achieve clinical remission by inducing and maintaining tolerance to offending allergens.[139] AIT is recommended as add-on therapy to standard of care, when clinically appropriate.[140] Common types of AIT available in the USA include subcutaneous (SCIT) and sublingual (SLIT). However, epicutaneous (transdermal) administration and intralymphatic injection (into a lymph node under ultrasound guidance) of allergen extracts are among novel modalities of delivery being explored.[141] Peptide immunotherapy is also being investigated and uses short synthetic peptides instead of whole proteins to reduce the allergenicity of immunotherapy preparations.[142] Emerging forms of immunotherapy may become an important future consideration in asthma management.

Systematic reviews and meta-analyses of SCIT have shown reduction of asthma severity, medication use, and airway hyper-responsiveness.[143–145] Studies also demonstrate that the use of SCIT for allergic rhinitis may inhibit the development of asthma. SLIT may be a safer alternative with less risk of systemic adverse reactions than SCIT.[144] Although there are more data to support the efficacy of SLIT in seasonal/perennial allergic rhinitis than in asthma,[146 147] SLIT can reduce airway hyper-responsiveness and decrease ICS dosing.[148 149] Benefits of AIT can persist for years after discontinuation.[140] However, more studies are needed on early use and efficacy of AIT in children with severe asthma. AIT is contraindicated in those with low FEV_1 and uncontrolled asthma.[150]

Immunomodulatory/biologic therapy

Immunomodulators help reduce inflammatory biomarkers associated in poorly controlled asthma. Here, currently approved and emerging biologic therapies are reviewed.

Anti-IgE therapy

Omalizumab is a recombinant anti-IgE IgG antibody that is injected every 2–4 weeks in patients with persistent allergic asthma.[151] Omalizumab can reduce exacerbations and corticosteroid use and is approved in children ≥6 years with severe, persistent allergic asthma.[152 153] Improvement in FEV_1 is also observed.[154] Reduced FeNO is seen in children on omalizumab therapy.[155]

Antieosinophilic therapies

Mepolizumab is an anti-IL-5 biologic that targets eosinophils and can be used in patients ≥6 years.[156] Mepolizumab can improve lung function and quality of life,[157] and reduce exacerbations, healthcare utilization, and corticosteroid use.[158]

Reslizumab targets IL-5 and is approved for severe eosinophilic asthma in children ≥12 years.[159] Studies show improved quality of life, lung function, and asthma control.

Reslizumab appears to be safe and effective, but data are limited to adolescents and adults and intravenous administration limits use.[159]

Benralizumab binds to IL-5 receptors and is approved for children ≥12 years.[160] Trials (efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta-2 agonist (SIROCCO),[161] benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA),[162] and oral glucocorticoid-sparing effect of benralizumab in severe asthma (ZONDA)[163] reported improved lung function, exacerbations, and blood eosinophils. Benralizumab decreases reliance on corticosteroids.[160]

Dupilumab is directed against the IL-4 receptor subunit alpha of IL-4 and IL-13 receptors and can be used in patients ≥12 years.[164] Dupilumab reduces corticosteroid use and exacerbations and improves lung function in moderate to severe asthma.[165–167]

Bronchial thermoplasty

Bronchial thermoplasty (BT) uses radiofrequency energy to generate heat that is applied through a flexible bronchoscope to the upper airway and smooth muscles that control constriction.[168]

This procedure may ameliorate chronic structural airway changes and improve quality of life.[168] In select adults, studies have shown improvement of asthma symptoms.[169] BT is not FDA-approved in children. At this time, the ATS recommends use of BT for severe asthma only in clinical studies.[170]

Emerging treatments for asthma for future consideration
Anti-thymic stromal lymphopoietin

Anti-thymic stromal lymphopoietin (TSLP) is implicated in inflammation in asthma. It augments Th2 response and release of IL-5, IL-6, and IL-13.[171] Activated airway epithelial cells in the lungs release TSLP in response to allergens, pathogens, or other insults to the airway epithelium.[171] High TSLP levels can be found in induced sputum specimens, lavage samples, and bronchial biopsies of patients with severe asthma.[172] Use of anti-TSLP therapy can reduce airway inflammation, hyper-responsiveness, and allergen-induced bronchoconstriction.[173] Tezepelumab, an anti-TSLP monoclonal antibody, can decrease exacerbations in adults with uncontrolled asthma.[174] TSLP appears to be a promising therapeutic strategy for allergic diseases and may also target non-eosinophilic inflammation.[174]

Siglec-targeting therapy

Siglecs (sialic acid binding immunoglobulin-like lectin or sialic acid binding Ig-like lectins) are membrane proteins that act as cell surface receptors to sialic acid-containing biomolecules and modulate cellular signaling.[175] Studies suggest siglecs as future therapeutic targets in severe asthma and other diseases with eosinophilic or neutrophilic inflammation.[176 177] The safety and efficacy of targeting siglec-8 and siglec-9 as viable therapeutic options in severe asthma are being investigated. Studies need to continue exploring the multiple underlying mechanisms, expression patterns, and physiological roles of siglecs.

Asthma Exacerbation [68, 181, 182]
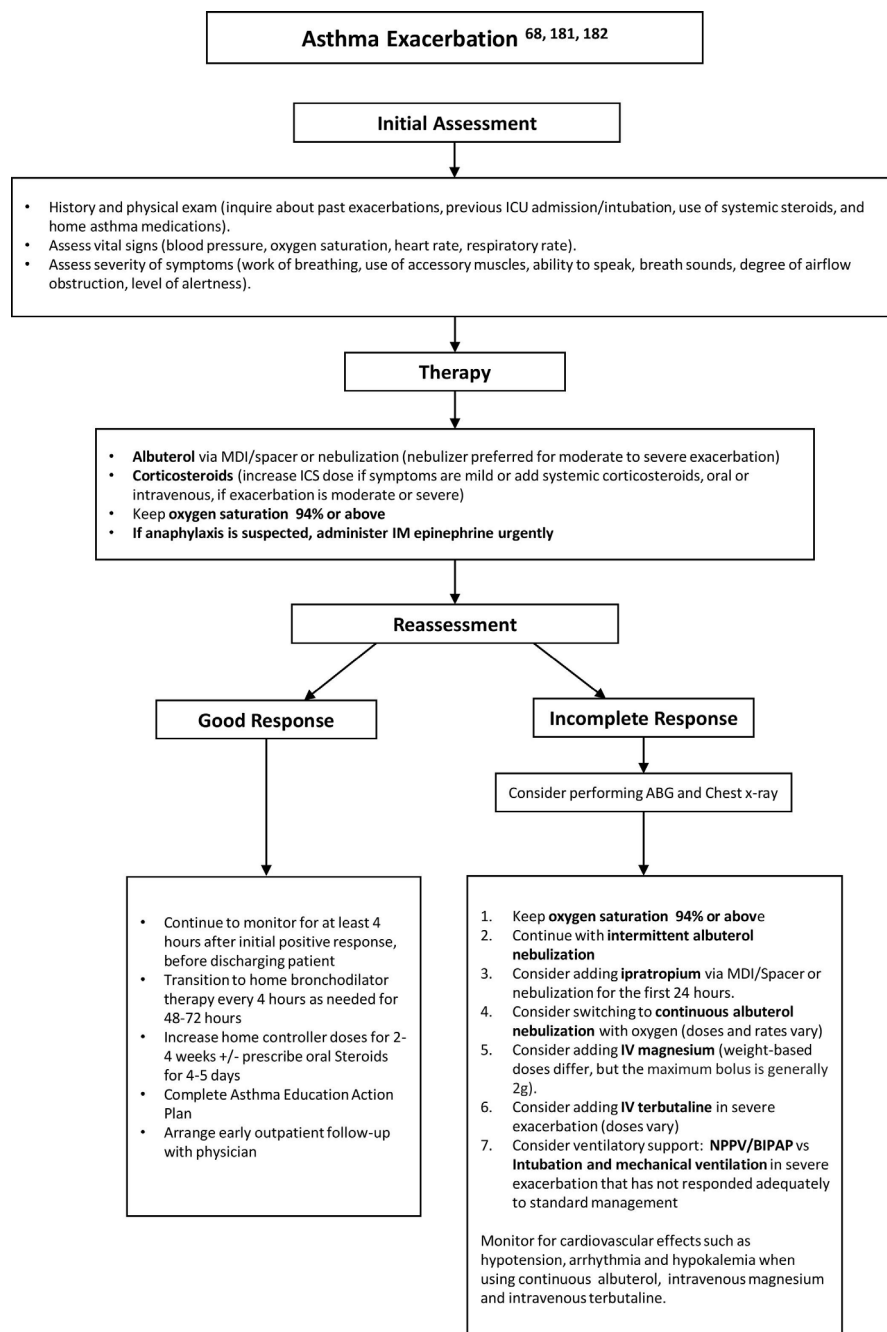
Figure 1 Hospital management of acute asthma exacerbation. ABG, arterial blood gas; BIPAP, bilevel positive airway pressure; ICS, inhaled corticosteroids; ICU, intensive care unit; IM, intramuscular; IV, intravenous; MDI, medium dose inhaler; NPPV, non-invasive positive pressure ventilation.

Prostaglandin D2 receptor antagonist/CRTH2 antagonists

Prostaglandin D2 (PGD2) plays an important role in the pathophysiology of asthma. Upregulation of the PGD2 pathway amplifies inflammatory immune response and induces tissue damage and remodeling in severe asthma.[178] Presently, the PGD2 receptor pathway is being studied as a potential therapeutic target for asthma.[179] Examples of drugs targeting this pathway include DP2 receptor antagonists (CRTH2 antagonists; chemoattractant receptor-homologous molecule expressed on Th2 cells) fevipiprant.[180] Preliminary results were promising with fevipiprant and

showed decreased eosinophilic inflammation in patients with moderate to severe asthma,[180] but phase III trials were not as favorable. Additional clinical developments targeting the PGD2 receptor pathway are underway.

Asthma exacerbations

Severe asthma exacerbations (figure 1) requiring an ED visit and/or inpatient hospitalization with potential need for intensive care are characterized by worsening alertness, hypoxemia, tachycardia, tachypnea, and signs of respiratory

compromise.[68] In children, oxygen saturation under 90% is an indication for aggressive management, as children often develop hypoxemia later than adults.[68] Supplemental oxygen can be titrated against need to achieve an oxygen saturation target range of 94%–98% in children.[68 181] Portable spirometers and peak flow meters can be used in acute asthma exacerbation to help assess airflow limitation, but may be challenging to obtain and may not be sensitive or reliable.[181] Chest radiographs and arterial blood gases can be performed in sicker patients where an alternative diagnosis or influencing factor is considered, but are not necessary in mild asthma exacerbations that have shown good response to initial management.[181 182] In addition, patients suspected of having a potential anaphylactic reaction should be promptly treated with intramuscular epinephrine.[181]

In an acute asthma exacerbation, corticosteroids and inhaled albuterol through a metered dose inhaler with a spacer or nebulization are used as first-line therapy. Ipratropium bromide can be considered in adjunct to improve response to initial therapy for the first 24 hours of exacerbation.[182] The addition of intravenous magnesium sulfate to inhaled beta-agonists and oral or intravenous corticosteroids has been found effective in the treatment of severe acute asthma exacerbation not responsive to initial therapies.[183–185] However, strong evidence and data are limited, and dosing regimens are varied.[186] Intravenous terbutaline is an additional adjunct option in severe asthma exacerbation, especially with impending respiratory failure.[187 188] A study by Doymaz et al[189] found that early administration of terbutaline may decrease requirement of invasive ventilator and respiratory failure with appropriate hemodynamic and metabolic monitoring. Currently, there is not enough evidence to firmly recommend routine use of intravenous terbutaline in acute asthma exacerbation in children.

Non-invasive positive pressure ventilation (NPPV), also referred to as bilevel positive airway pressure, has been used in severe asthma exacerbations to help improve gas exchange and work of breathing in children.[182 190] Due to lack of evidence, a 2016 Cochrane review could not reach a conclusion on the benefits and harms of NPPV as add-on therapy to the standard management of acute asthma exacerbation in children; however, NPPV can be used as a bridge to avoid intubation if the child does not meet criteria for immediate invasive artificial airway.[191] In severe, life-threatening asthma attacks, endotracheal intubation and mechanical ventilation may become necessary, and specific ventilatory considerations to avoid complications should be considered. Ventilator modes that minimize hyperinflation and allow for prolonged expiratory times are recommended.[192 193]

Adherence

Adherence to therapy improves quality of life and reduces asthma morbidity, mortality, and healthcare utilization costs.[194] If suboptimal adherence is not uncovered, patients can be miscategorized on the disease spectrum and receive unnecessary escalation of therapy. Good communication and relationship between healthcare providers and patients is crucial.[195] It facilitates shared decision making and encourages patient/caregiver involvement.[196] Clinic visits provide a unique opportunity for strengthening patient–provider partnership, for education, positive reinforcement, and affirmation, and adherence should be assessed at every visit.[195] Attitudes toward treatment can be assessed, while concerns are addressed and misunderstandings clarified.[197] Simplifying treatment regimens is often helpful.

TECHNOLOGY IN ASTHMA MANAGEMENT

The number of digital health technologies has increased significantly over the years and the attractiveness of digital tools usually varies based on available functions and the quality of features offered.[198] High-quality interactive mobile health (mHealth) applications have the potential to empower patients and expand asthma self-management.[199] They can improve asthma control, adherence, and inhaler technique.[200] Digital tools such as asthma smart inhalers and mobile sensors allow patients to store usage, record peak flow values, and better control their symptoms by tracking air quality and environmental triggers.[200] Key initiatives can further empower developers and explore how available mobile platforms can better engage users and support asthma self-management according to national medical guidelines. Patients and their providers should be cautious when selecting apps to use.

CONCLUSION

Effective multimodal strategies and comprehensive interventions tailored to individual characteristics and a commitment to address risk factors, modifiers, and disparities implicated in poor asthma control may help reduce the uneven burden of asthma in children in the USA. An improved understanding of asthma pathobiology can further advance therapeutics and individualize therapy. This paper sought to provide a review for practitioners on severe pediatric asthma. Although approaches exist for diagnosis and treatment of asthma, management of severe asthma remains difficult. Limited studies in the pediatric population add to this challenge. More studies should investigate the safety and efficacy of evolving therapeutics in children.

and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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