A Practical Approach to Severe Asthma in Children

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Abstract

Severe asthma accounts for only a small proportion of the children with asthma but a disproportionately high amount of resource utilization and morbidity. It is a heterogeneous entity and requires a step-wise, evidence-based approach to evaluation and management by pediatric subspecialists. The first step is to confirm the diagnosis by eliciting confirmatory history and objective evidence of asthma and excluding possible masquerading diagnoses. The next step is to differentiate difficult-to-treat asthma, asthma that can be controlled with appropriate management, from asthma that requires the highest level of therapy to maintain control or remains uncontrolled despite management optimization. Evaluation of difficult-to-treat asthma includes an assessment of medication delivery, the home environment, and, if possible, the school and other frequented locations, the psychosocial situation, and comorbid conditions. Once identified, aggressive management of issues related to poor adherence and drug delivery, remediation of environmental triggers, and treatment of comorbid conditions is necessary to characterize the degree of control that can be achieved with standard therapies. For the small proportion of patients whose disease remains poorly controlled with these interventions, the clinician may assess steroid responsiveness and determine the inflammatory pattern and eligibility for biologic therapies. Management of severe asthma refractory to traditional therapies involves considering the various biologic and other newly approved treatments as well as emerging therapies based on the individual patient characteristics.

Keywords: problematic severe asthma; pediatric asthma; difficult-to-treat asthma; asthma evaluation; asthma management

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Pediatric severe asthma accounts for only 2 to 5% of childhood asthma (1, 2) but a large proportion of the costs, resource utilization, and morbidity (3). The American Thoracic Society and the European Respiratory Society define severe asthma as that which requires treatment with high-dose inhaled corticosteroids plus a second controller throughout the previous year and/or systemic corticosteroids for 50% of the previous year, to prevent it from becoming "uncontrolled," or asthma that remains "uncontrolled" despite this therapy (1).

Children with poor asthma control despite maximal prescribed therapy are a heterogeneous group (4). Proper confirmation of the diagnosis, a comprehensive outpatient evaluation including differentiation between difficult-to-treat asthma and severe asthma that is resistant to traditional therapies, and optimization of management are essential to reduce morbidity and healthcare costs. The majority of literature on evaluation and management of pediatric severe asthma are based in European health systems (4, 5), and application of adult guidelines is not appropriate; children with severe asthma have more atopy, higher male prevalence (until adolescence), less airflow limitation, and less association with obesity (6, 7). This pragmatic review highlights the necessary steps to ensure proper diagnosis and effective management of these difficult cases, discusses current areas of debate in characterization of asthma in this population, and provides updated information on U.S. Food and Drug Administration (FDA)–approved therapeutics (Figure 1).

Step 1: Diagnosis Confirmation

Studies have demonstrated that as many as 30% of referrals for severe asthma are misdiagnosed (8). Numerous alternative conditions can masquerade as asthma, including vocal cord dysfunction, anatomic abnormalities such as tracheobronchomalacia, and other obstructive lung diseases such as cystic fibrosis and bronchiolitis obliterans (Table 1).

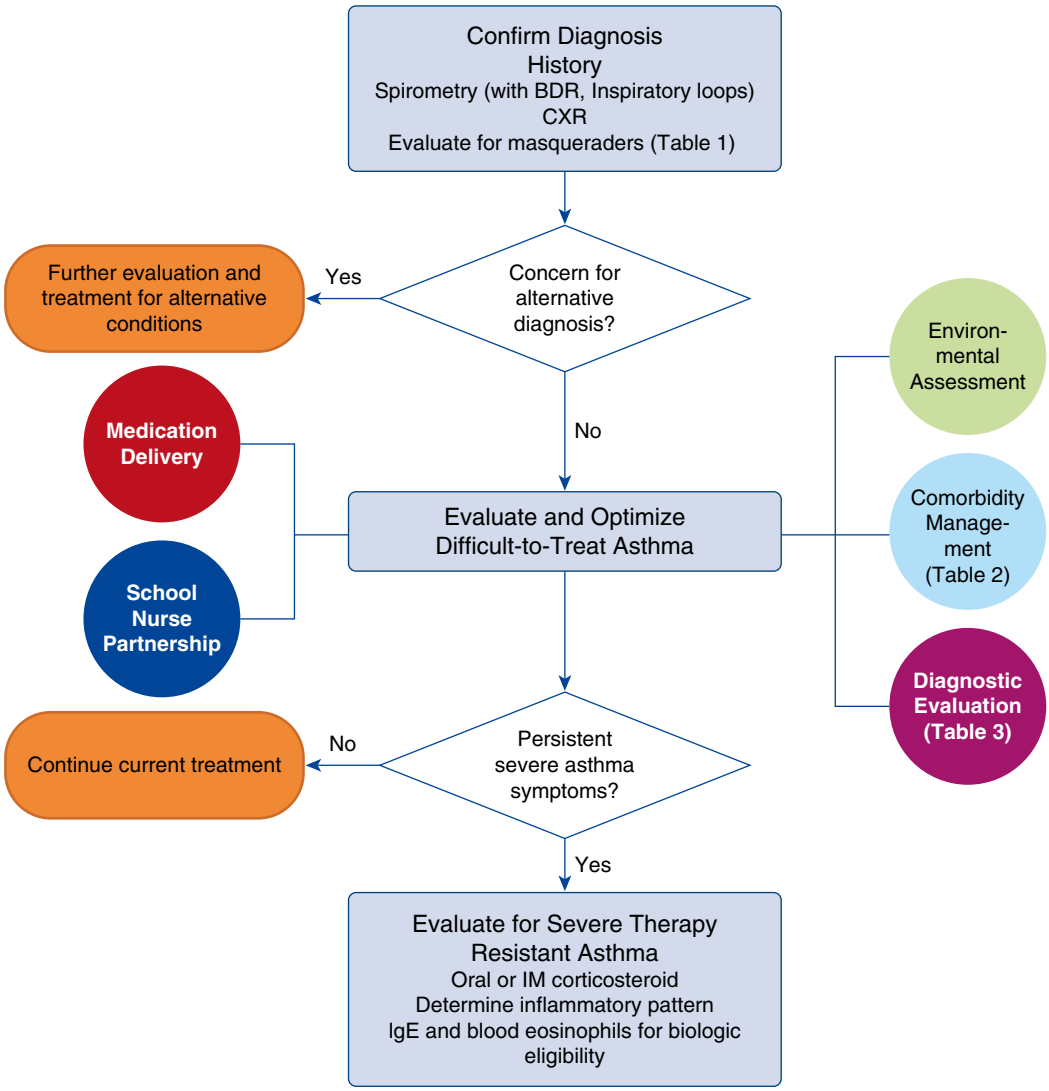

Figure 1. Step-wise algorithm for the evaluation and management of the pediatric patient with severe asthma. BDR = bronchodilator response; CXR = chest X-ray; IgE = immunoglobulin E; IM = intramuscular.

Diagnosis confirmation can be accomplished through detailed history, physical examination, and spirometry. The goal of this should be twofold: *1*) to elicit supporting evidence for asthma, including evaluation of triggers and airway hyperreactivity; and *2*) to identify features that might suggest alternative diagnoses. Providers should inquire regarding episodic symptoms of airflow obstruction or airway hyperresponsiveness, including cough, nighttime awakening, wheezing, chest tightness, shortness of breath, and exercise intolerance (1). Pre- and post-bronchodilator spirometry should be obtained, preferably in the context of withholding any short- or long-acting bronchodilator, to assess obstruction and bronchodilator responsiveness (1, 4). Inspiratory flow–volume curves help identify fixed or dynamic central airway obstruction; however, it is important to note that spirometry is neither sensitive nor specific for diagnosing vocal cord dysfunction (9). A 12% and 200-ml increase in the forced expiratory volume in 1 second (FEV_1) or forced vital capacity is diagnostic of bronchodilator reversibility (10); however, improvements in FEV_1 of 8% in the appropriate context may be more sensitive to support the diagnosis of asthma in children (11). If no obstruction is present, bronchoprovocation testing with methacholine or exercise should be performed (1, 12, 13).

A chest radiograph should be considered to evaluate for anatomic abnormalities of the heart, airways, and lung parenchyma that may suggest an alternate diagnosis. Additional investigations for evaluation of alternative diagnoses (Table 1) should be guided by clinical suspicion or atypical presentations (1, 2, 5), such as the presence of a productive cough, stridor, absence of atopy, or rapidly declining lung function. In these cases, diagnostic testing to consider include lung volumes to evaluate for air trapping, sweat test, airway and parenchyma evaluation by bronchoscopy with bronchoalveolar lavage, and high-resolution computed tomographic (CT) imaging of the chest, among others.

In children younger than 6 years of age, the diagnosis of asthma is more challenging.

Table 1. Masqueraders of asthma: categories of lung disease to consider in the differential diagnosis, with examples

Dysfunctional breathing
Vocal cord dysfunction
Panic attacks
Anatomic
Tracheobronchomalacia
Tracheoesophageal fistula
Central airway compression or obstruction (e.g., vascular rings, mediastinal mass)
Suppurative lung diseases
Cystic fibrosis
Primary ciliary dyskinesia
Bronchiectasis
Protracted bacterial bronchitis
Interstitial lung disease
Bronchiolitis obliterans
Bronchopulmonary dysplasia
Immune dysfunction/rheumatologic disorders
Hypogammaglobulinemia
Eosinophilic granulomatosis with polyangiitis
Connective tissue disease
Other
Foreign body aspiration
Chronic aspiration
Congenital heart disease

Although up to 40% of preschool children in the United States have wheezing, a minority go on to develop asthma (14). This suggests a higher likelihood of alternative etiologies for recurrent wheezing in younger children, and it is therefore particularly important to assess for possible masqueraders of asthma in young children, such as aspiration and tracheobronchomalacia. The diagnosis of asthma in preschool children is often based on history and treatment response, because of the lack of reliable lung function assessment.

Although there is evidence preschool-age children can perform pulmonary function tests in the appropriate environment with coaching, reference data and bronchodilator reversibility thresholds are currently lacking (15). Forced oscillation technique, among other effort-independent tests, may be promising in young children but also require development of normative values and diagnostic thresholds (15).

Step 2: Evaluation and Optimization of Difficult-to-Treat Asthma

Once confirmed, the next step is to differentiate between difficult-to-treat asthma, which is asthma that can be controlled with appropriate management, and asthma that requires the highest level of therapy or remains uncontrolled despite optimal management (2, 5). This portion of the evaluation involves identifying potential modifiable factors leading to poor control, addressing them, and evaluating clinical response. Up to 55% of patients referred for severe asthma will ultimately fall into the difficult-to-treat category (16).

Medication Delivery Assessment

Adherence. Objective assessment of medication adherence and administration technique is essential. Eighty percent adherence to inhaled corticosteroids is standardly acceptable (4) and considered optimal for maintaining control as measured by symptoms, activity limitation, and exacerbations (17). However, only one-fourth of children achieve this level of compliance (18), and patients and caregivers grossly overestimate adherence (18, 19). There are a variety of objective methods to assess compliance, including pharmacy record review, dose counters, canister weights, and electronic monitoring devices. Pharmacy record review is widely used, simple, and cost effective, but its accuracy can be limited by medication stockpiling and lacks details of actual drug administration. Canister weight can quantify doses administered and is relatively inexpensive but can be inaccurate in the case of dose dumping. Electronic monitoring devices provide accurate data on date, time, and sometimes location of use, via pressure-actuated monitoring of metered-dose inhalers (20, 21), but presently their availability is limited. A pediatric study of inhaled corticosteroid adherence suggests that electronic monitoring devices may provide a more accurate assessment of adherence rates, estimated at 52%, in comparison with 70% by prescription refill data and 98% by self-reporting (19). This highlights the need for objective measures of adherence. However, there is currently insufficient evidence to determine if the improved accuracy of electronic monitoring devices outweighs higher cost, need for patient education, and potential device failure (19, 22).

Technique. Improper medication administration technique is also prevalent and problematic. Less than one-fourth of children can demonstrate proper inhaler technique (23), and many lack appropriate supervision. By age 11 years, 50% of children assume responsibility for administering their own asthma medications unsupervised (24).

It is important to determine appropriateness of the mode of delivery for the child's age and development. For example, the efficacy of a dry powder inhaler is dependent on the child's ability to generate sufficient peak inspiratory flow, which is approximately age 4 years for a low-resistance device such as a Diskus and age 9 years for a high-resistance device such as a Turbohaler (25), but can vary significantly depending on the individual child. For metered-dose inhalers, wide consensus supports the use of valved holding chambers. Although a recent study showed no difference in severe exacerbation rates with and without valved holding chambers (26), more evidence will be required before considering a change in clinical practice.

Medication Delivery Optimization

Clinic. A simple intervention to capture information about medication use and technique is to request that all asthma medications be brought to every visit. This allows the clinical team to *1*) identify which medications the patient is actually taking—many families will have tried several medications by the time they are referred to subspecialty care, leading to potential confusion; *2*) determine if the medication has surpassed expiration dates; and *3*) allow for assessment and review of administration technique with the patient's own medicine. Reinforcing proper delivery at each visit is important, as a patient's technique wanes between teaching sessions (27).

Partnership with the school nurse. Children spend a significant amount of time at school, which can be leveraged to address asthma care and educational needs (28–31). The school nurse can play a valuable role in care coordination, education, medication adherence, identification of worsening symptoms, and monitoring asthma control (28, 29, 31). Active participation in asthma management by the school nurse can improve school absenteeism and potentially decrease the frequency of emergency room visits (30–32). Directly observed administration of a single daily dose of inhaled corticosteroids in the school setting has been shown to improve asthma

control and decrease asthma-related school absences, nighttime asthma symptoms, use of rescue medications, and disruptions to family plans (28, 30, 32). This approach should be considered in patients with severe asthma, particularly if adherence is questionable. Some schools may not have full-time nurses or may share one nurse among multiple facilities, which makes such collaborations challenging (29).

Use of technology. Because medication adherence is linked to improved asthma control (33), there is increasing interest in using technology to assist with adherence. Electronic monitoring devices have the capability to both track adherence and provide patients with reminders. Although studies have linked their use to increased adherence, they have not been shown to improve asthma outcomes (34, 35). Similarly, there are insufficient data to suggest that telecommunication or text messaging interventions result in sustained improvements in asthma control (36, 37). Smart-phone applications and wearable monitors are also emerging technologies for chronic asthma disease management but have not yet made it into routine clinical practice.

Environmental Assessment

A home environmental assessment provides an opportunity to identify and reduce inciting triggers, such as dust mites, molds, pets, pests such as cockroaches or mice, and irritants such as secondhand smoke or other pollutants (38). Home visits focusing on environmental and educational assessments and interventions are both clinically successful and cost effective (39). As almost 95% of pediatric patients with severe asthma have allergen sensitivity (7), this intervention should be integral in evaluation and management.

The Inner City Asthma Study demonstrated improvements in morbidity in sensitized patients with asthma by reducing indoor allergens through multifaceted interventions targeting allergens through integrated pest management, high-efficiency particulate air vacuum cleaners, high-efficiency particulate air filter air cleaners, and dust mite–impermeable bedding covers (40). Importantly, they demonstrated sustained reduction in asthma symptoms and healthcare utilization, which have since been replicated (41). Mite-impermeable bedcovers alone have recently been shown to reduce exacerbations in dust mite–sensitive children with a prior exacerbation (42).

Toxic exposures to indoor air pollutants, such as nitrogen dioxide and particulate matter, and chemicals used for cleaning, deodorizing (43), or pest management (44) are known airway irritants. Many have been directly associated with increased respiratory symptoms and decreased lung function (45). Indoor air pollution can be generated from combustion heating and cooking. These pollutants can become concentrated in living spaces with poor ventilation, and particles are easily resuspended with common household activities. Part of home environmental assessments and interventions for patients with severe asthma should include assessment of these sources of pollutants and aerosolized products and modifications to diminish their presence. This may take the form of adding or encouraging use of exhaust fans above gas ranges and using natural cleaning supplies. Use of aerosols for deodorization should be discouraged. Environmental tobacco smoke is a potent trigger for most patients with asthma and should be avoided. There is an association between chronic environmental tobacco smoke and asthma exacerbations, although causality has not been proven (46). Data are inconclusive regarding the impact of behavioral interventions on either reduction in caregiver smoking or on improved outcomes in children with asthma (47), possibly because smoking cessation is so difficult to achieve. Nevertheless, smoking cessation should be the goal, as family members smoking away from the child still leads to substantial tobacco exposure for the patient (48).

Although the home environment has been extensively studied, the school environment is less well understood but extremely important, as children spend up to 8 h/d in this environment. Several studies have demonstrated that the school/classroom environment is also a source of significant allergen exposure (49–51). Clinical assessments should specifically elicit if symptoms worsen during the school year or in specific classrooms or improve on school vacations. Evaluation of school-based environmental interventions to improve asthma morbidity, such as air purifiers and integrated pest management, is currently underway (ClinicalTrials.gov: NCT02291302) (52).

Assess Comorbid Conditions

Numerous comorbidities have been associated with asthma severity and may contribute directly to risk of poor asthma control and exacerbations (Table 2). Rhinosinusitis, symptomatic gastroesophageal reflux disease, and obesity are among the most prevalent, all of which are associated with increased exacerbation frequency (53), and their management should be optimized. Antacid therapy in patient without symptoms of gastroesophageal reflux disease does not improve asthma control (54), potentially increases risk of respiratory infections, and is therefore not recommended.
The interplay of asthma and obesity is complex and not fully understood. There are many factors involved, including alterations in inflammatory pathways (55), deconditioning, and abnormal pulmonary mechanics (56). Obstructive sleep apnea (OSA) has been associated with asthma, and treatment of OSA with adenotonsillectomy may improve asthma control (57). Vocal cord dysfunction is often comorbid with asthma, and interventions for both are frequently required (58).

The role of vitamin D supplementation is an area of ongoing controversy and research. Testing for vitamin D is expensive, and the effects of supplementation in a severe asthma population are still not determined.

Psychological Assessment

Asthma is associated with increased rates of psychiatric comorbidity (59), and the two interact in a bidirectional manner. Psychosocial stressors and psychiatric problems can impact asthma control in almost half of cases by decreased

Table 2. Comorbid conditions that may coexist with asthma and lead to poor control

Rhinosinusitis
Symptomatic gastroesophageal reflux disease
Vocal cord dysfunction
Obesity
Obstructive sleep apnea
Eosinophilic esophagitis
Allergic bronchopulmonary aspergillosis
Psychiatric conditions, such as anxiety and depression

adherence, increased symptom reporting, and possibly increased airway inflammation (60). Recent evidence demonstrates the biologic basis of neural triggering by emotional stimuli leading to airway obstruction using functional magnetic resonance imaging (61). Emotional triggers for asthma should be validated in the patient and addressed as any significant contributing trigger. It is important to assess for psychiatric comorbidity in both the patient and caregivers; mothers with high ratings of depressive symptoms are 40% more likely to take their children to the emergency department for asthma (62), have lower medication adherence rates, and are less able to cope with their children's asthma (63). In addition, environmental stressors and violence in the home and neighborhood contribute to poor asthma control (64) and should assessed.

A detailed mental health assessment should be completed for patients and caregivers. Unfortunately, there is no standard comprehensive screening tool available. For this reason, a multidisciplinary asthma care team should include a trained mental health provider.

Diagnostic Testing

During the assessment of difficult-to-treat asthma, several laboratory investigations should be considered to determine the risk of addressable comorbidities and inflammatory phenotyping to determine eligibility for biologic therapies, if indicated (Table 3). For all children with severe asthma, complete blood counts to evaluate for eosinophilia, as well as total immunoglobulin E (IgE) and either specific IgE or skin-prick testing to common environmental allergens and known exposures should be sent. Typically, this should include sensitization to dust, molds, pests, and furred pets, as well as trees and grass pollens, although the specific items will vary by region. Highly elevated total IgE greater than 1,000 IU/μl should prompt consideration for allergic bronchopulmonary aspergillosis. For children with a history of recurrent infections, a more comprehensive immunologic evaluation including immunoglobulin levels should be obtained.

Table 3. Diagnostic evaluation

Standard Evaluation to be Conducted for All Pediatric Patients with Severe Asthma Referred for Specialist Evaluation	Additional Evaluation to be Considered on the Basis of Individual Patient Assessment
Pre/post spirometry	Inspiratory loops
Complete blood cell count with differential	Lung volumes
Immunoglobulin E	Sweat test
Specific immunoglobulin E or skin-prick test	Immunoglobulin levels
	Computed tomographic imaging of the chest
	Computed tomographic imaging of the sinuses
	Flexible bronchoscopy
	Direct laryngoscopy
	Esophagogastroduodenoscopy
	Polysomnography
	Adrenal insufficiency screening

Additional testing should be individualized and can include sinus CT scans for evidence of occult sinus disease, direct laryngoscopy and bronchoscopy for airway abnormalities, endoscopy for gastroesophageal reflux disease and eosinophilic esophagitis, and polysomnography for sleep-disordered breathing.

Evaluation of Steroid Side Effects

Although there is no standard guidance for evaluation of steroid side effects, by definition patients with severe asthma will have been on high-dose inhaled steroids or systemic steroids for an extended period of time. It is important to consider monitoring for adrenal insufficiency, bone demineralization, growth impairment, and immunosuppression. Morning cortisol and cortisol stimulation assays are the optimal measures of adrenal function. However, they can be logistically challenging. In instances when they cannot be performed, a screening dehydroepiandrosterone sulfate can be considered, which provides a diurnal-independent assay of the hypothalamic-pituitary-adrenal axis function. If normal, adrenal insufficiency is very unlikely (65). If any of these tests are abnormal, or if there is any other concern, a referral to endocrinology should be considered. Bone mineral density and ophthalmologic examinations are not routinely used to screen for steroid side effects from inhaled steroid exposure but should be considered for patients on long-term systemic steroids.

Step 3: Assessment and Management of Severe Asthma Refractory to Traditional Therapy

A subset of patients continue to require the highest level of asthma therapy to maintain control or their disease remains uncontrolled, despite the management optimization discussed above. They warrant additional evaluation and therapeutic intervention.

Evaluation

Glucocorticoid responsiveness testing. Intramuscular triamcinolone or observed oral corticosteroid can help determine whether additional steroid therapy is indicated (1). Up to 20% of children show significant improvement with additional steroids (6, 66), and up to 80% show a partial response (66, 67). Because of disease heterogeneity, improvement after steroid administration should be assessed in multiple domains: symptoms, spirometry, and markers of airway inflammation such as fractional exhaled nitric oxide or sputum eosinophils (67). Although the utility of this assessment in clinical practice is debatable, one clear piece of information that can be gleaned is to identify patients in whom further escalation of steroid therapy is unlikely to lead to clinical improvement.

Inflammatory pattern determination. There are several possible methods for evaluating inflammatory patterns in airway disease. However, pediatric data are limited and clinical utility has not yet

been shown, and therefore none are routinely implemented (2). There is some emerging evidence that use of fractional exhaled nitric oxide in pediatric asthma management may decreased exacerbations but does not affect inhaled steroid dose or asthma symptoms (68). It therefore may be useful in a subset of patients with severe asthma with frequent exacerbations but is not currently recommended for all children with severe asthma (68). Sputum eosinophil levels do not remain stable over time in children and therefore should not guide therapy (69). Exhaled breath condensate requires further validation (2). Similarly, flexible bronchoscopy may help identify the inflammatory profile (70), but data to support therapeutic decisions on the basis of these findings remain lacking.

Assessment for biologic therapy eligibility. For children who remain suboptimally controlled on high-dose inhaled steroids or are suffering from or are at high risk for side effects, screening for eligibility for biologic agents is the next step. If it has not already been done, absolute eosinophil count, total IgE, and allergen sensitivity testing should be obtained.

Management

Standard therapies

For refractory disease requiring step 5/6 of National Heart, Lung, and Blood Institute–based therapy (71), there are a number of additional therapies to consider. At this stage, an asthma specialist should be involved in management.

Oral corticosteroids. Patients who demonstrate an improvement or clinical response to intramuscular triamcinolone may derive additional benefit from chronic daily systemic steroids. Although there is no guidance for chronic steroid dosing, the lowest effective dose should be used, with consideration for alternate-day dosing to minimize side effects. Patients who exacerbate with attempts at weaning off should transition to a biologic or other therapy to minimize long-term side effects.

Tiotropium. Tiotropium is a long-acting anticholinergic bronchodilator approved by the FDA for ages 6 years and older. In adults, it has been shown to improve lung function and decrease exacerbations and is noninferior to long-acting beta agonist (72). Two recent pediatric studies demonstrated good safety and tolerance profiles and suggest an improvement in maximal FEV_1 (73, 74). The pediatric studies lacked consensus on optimal dosing (2.5 μg versus 5 μg) and significant improvement in symptoms and exacerbation rate. As pediatric asthma is particularly exacerbation prone, this lack of exacerbation reduction is particularly worrisome. Practically speaking, tiotropium offers a long-acting bronchodilator, which may benefit patients with severe asthma at risk of β-receptor downregulation due to overuse of short-acting β-agonists. It may be particularly useful in nonatopic patients who are less likely to benefit from biologics (75).

Approved biologic agents. There are currently three monoclonal antibody therapies approved by the FDA for children younger than 18 years of age with severe asthma. Omalizumab is anti-IgE and approved for ages 6 years and older. Mepolizumab and benralizumab are anti–interleukin (IL)-5 drugs approved for 12 years and older. Reslizumab is an aniti–IL-5 drug with FDA approval for adults 18 years and older. Table 4 outlines mechanisms of action, applicable population, dosing, outcome data, and adverse effects. When choosing between biologics, there are a number of considerations, including the patient's age, degree of eosinophilia, IgE elevation, frequency and route of administration, and body habitus (reslizumab is weight based and therefore may be preferable in obese patients). In moderate or severe persistent asthma, omalizumab reduces exacerbations by 40%, almost eliminates the seasonal spikes in exacerbations, decreases inhaled steroid and long-acting β-agonist use, and increases symptom-free days (76). Patients with comorbid IgE-driven conditions, such as urticaria, eczema, food allergy, and allergic rhinitis, may derive secondary benefit from omalizumab (77). However, omalizumab may have some benefit in nonatopic patients (78) as well. In severe eosinophilic asthma, mepolizumab was found to have a comparable 47% reduction in exacerbations, a reduction in oral corticosteroid use, and symptom improvement (79). Similar reductions in exacerbation rate and oral corticosteroid use were found with benralizumab, with additional improvement in lung function (80). The IL-5 antagonists should be considered particularly in patients with eosinophilia and those who cannot be weaned from oral corticosteroids. Head-to-head comparison trials of these drugs are lacking, but the decrease in exacerbation rate appears similar (76, 79–81).

Additional Therapeutic Considerations: Emerging, Experimental, or Insufficient Evidence

Increased inhaled corticosteroids during exacerbations. There are no clinical trials investigating the efficacy of increasing inhaled steroid dosing during exacerbations in pediatric severe asthma. However, studies in mild and moderate persistent asthma have found insufficient evidence for a reduction in adverse events or need for oral corticosteroids (82). Single-inhaler therapy with inhaled corticosteroids/formoterol for both maintenance and quick relief therapy is efficacious in adults. For children older than 12 years with persistent asthma, it may reduce hospitalizations, emergency department visits, and oral corticosteroids. However, the risk of serious adverse effects remains unclear, and the current evidence is therefore insufficient to recommend standard implementation (83). By extrapolation, acute increase in inhaled steroids should not standardly be implemented in pediatric severe asthma.

Theophylline. Theophylline is a bronchodilator and antiinflammatory that accelerates neutrophil apoptosis (5) and may improve steroid sensitivity (84). These characteristics suggest it could be beneficial to patients with asthma with neutrophilic airway inflammation; however, supportive clinical data in severe asthma are lacking, and frequent drug level monitoring complicates its use.

Biologics. There are a number of additional biologic therapies under investigation, including dupilumab (anti–IL-4 receptor α), which are currently in phase III trials for children 12 years and older. An in-depth discussion is beyond the scope of this review but can be found in a recent review by Katial and colleagues (80).

Antimicrobial drugs. Current European Respiratory Society/American Thoracic

Table 4. U.S. Food and Drug Administration–approved biologic drugs for pediatric severe asthma

Drug	Mechanism of Action	Dosing (Route)	Applicable Population	Clinical Outcomes	Potential Serious Side Effects
Omalizumab (Xolair) FDA approved 2002	Anti-IgE mAb Binds IgE Fc region Prevents binding to mast cells/basophils	150, 225, 300, or 375 mg Q2W or Q4W (SC); based on weight and IgE	Age ⩾ 6 yr Moderate to severe asthma and perennial aeroallergen sensitization IgE 30–700 (age 6–11) yr IgE 30–1,300 (age ⩾ 12) yr	**↓Exacerbation frequency** ↓Symptoms **↓ICS dose** ↑FEV_1 ↑QOL	Anaphylaxis (up to 0.2%) Not associated with malignancy in postmarketing safety study (92)
Mepolizumab (Nucala) FDA approved 2015	Anti–IL-5 mAb Inhibits IL-5 binding to α-subunit of IL-5 receptor complex on eosinophils Inhibits growth, differentiation, recruitment, activation, and survival of eosinophils	100 mg Q4W (SC)	Age ⩾ 2 yr Severe eosinophilic asthma Blood eosinophil count ⩾ 150 cells/μl within 6 wk or >300 in past 12 mo	**↓Exacerbation frequency** ↓Symptoms **↓OCS dose** ±FEV_1 ↑QOL	Hypersensitivity reactions Herpes zoster
Reslizumab (Cinqair) FDA approved 2016	Anti–IL-5 mAb Inhibits IL-5 binding to α-subunit of IL-5 receptor complex on eosinophils Inhibits growth, differentiation, recruitment, activation, and survival of eosinophils	3 mg/kg Q4W (IV)	Age ⩾ 18 yr Severe eosinophilic asthma Blood eosinophil count ⩾ 400 cells/μl*	**↓Exacerbation frequency** ↓Symptoms **↑FEV_1** ↑QOL	Anaphylaxis (0.3%) Transient ↑CPK Note: patients aged 12–18 yr had higher rate of exacerbations than placebo
Benralizumab (Fasenra) approved 2017	Anti–IL-5 mAb Simultaneously binds Fc receptor on NK cells depleting eosinophils by antibody-dependent cell-mediated cytotoxicity and apoptosis	30 mg Q4W × 3 doses, then Q8W (SC)	Age ⩾ 2 yr Severe eosinophilic asthma Blood eosinophil count ⩾ 300 in past 12 mo and two or more exacerbations*	**↓Exacerbation frequency** ↓Symptoms **↓OCS dose** **↑FEV_1**	Patients with Helminth infections excluded from clinical trials—may interfere with infection clearance Hypersensitivity reactions

Definition of abbreviations: CPK = creatine phophokinase; Fc = fragment crystallizable; FDA = U.S. Food and Drug Administration; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IgE = immunoglobulin E; IV = intravenous; mAB = monoclonal antibody; NK cell = natural killer cell; OCS = oral corticosteroids; QOL = quality of life; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
*Phase III trial entry criteria, not part of labeled indication definition.
Bold text indicates key clinical findings.

Society guidelines recommend against routine use of macrolides for children with severe asthma (1). Overall, in children with persistent or severe asthma, macrolides have not been shown to have an effect on symptoms or exacerbation rates (85). However, there is some evidence that they can result in a possible reduction in daily oral corticosteroid use and improvement in FEV_1 (85, 86) and may also be useful in noneosinophilic asthma (85). Furthermore, in adults with noneosinophilic severe asthma, macrolides may decrease rates of severe exacerbations and lower respiratory tract infections (87). In addition, episodic azithromycin is beneficial to preschool-aged children with frequent exacerbations (88). Currently, although data are insufficient to recommend routine use in pediatric severe asthma, macrolides may be considered in children with refractory disease, oral corticosteroid dependence, noneosinophilic inflammation, or recurrent lower respiratory tract infections. The data regarding use of antifungals for fungal sensitization in severe asthma (excluding instances of allergic bronchopulmonary aspergillosis) are mixed, and antifungals are therefore not currently recommended (89).

Immunosuppressants. There are currently insufficient data to support the use of steroid-sparing agents such as azathioprine, cyclosporine, or methotrexate in children with severe asthma.

Allergen immunotherapy. Immunotherapy improves asthma control in children with mild to moderate asthma, but the requirement for patients to have stable asthma because of the risk of severe reaction (90) severely limits its practicality in patients with severe asthma.

Surgical interventions. Bronchial thermoplasty is not currently recommended or approved for children or adolescents but has had some success in adults (91).

Step 4: Efficacy Assessment

Patients with severe asthma should be followed by specialists at least quarterly. As severe asthma is a heterogeneous condition, the outcome measures of interest will be based on patient phenotype—whether reduction of exacerbations, improvement in daily

symptoms, improved lung function, or any combination of these. It is not reasonable to expect the same degree of control as in mild or moderate persistent asthma. A compromise must be made between patient safety, treatment burden, and quality of life. Practically speaking, outcome measures should include spirometry, severe exacerbations, and healthcare utilization.

Conclusions

Pediatric severe asthma is a heterogeneous disorder. Its evaluation requires a careful confirmation of the diagnosis, followed by a differentiation into difficult-to-treat versus severe asthma refractory to traditional therapies. Successful management involves optimization of medication delivery, comorbidities, the school and home environment, and targeted individualized therapies, including the use of newer steroid-sparing agents such as biologics and tiotropium. Practical application of these principles requires a multidisciplinary approach that is able to assess and intervene to improve the patient's asthma in the clinical, home, and, often, school environment. ■

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