

The Tempest: Difficult to Control Asthma in Adolescence



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Gregory T. Burg, MD, Ronina Covar, MD, Alyssa A. Oland, MD, and Theresa W. Guilbert, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To be able to identify biologic therapies approved for use in adolescents with severe asthma.
2. To understand that adolescents with severe asthma face a number of challenging psychosocial issues that in turn complicate their management.
3. To be aware of potential emerging or future therapies that may soon be available to adolescents with severe asthma.
4. To understand that asthma is a heterogeneous disorder and that phenotype-based therapies may lead to better outcomes.

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Severe asthma is associated with significant morbidity and is a highly heterogeneous disorder. Severe asthma in adolescence has some unique elements compared with the features of severe

asthma a medical provider would see in younger children or adults. A specific focus on psychological issues and adherence highlights some of the challenges in the management of asthma in adolescents. Treatment of adolescents with severe asthma now includes 3 approved biologic phenotype-directed therapies. Therapies available to adults may be beneficial to adolescents with severe asthma. Research into predictors of specific treatment response by phenotypes is ongoing. Optimal treatment strategies are not yet defined and warrant further investigation. © 2018 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2018;6:738-48)

Key words: Severe asthma; Adolescent; Phenotype; Biologics; Difficult-to-treat asthma; Adherence; Psychosocial

CASE 1

JG (*fictitious initials have been used for all patients to protect their identities*) is a 13-year-old black male with severe persistent asthma seen in a severe asthma clinic with a concerning history of recurrent

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Abbreviations used

ACT- Asthma Control Test
ATS- American Thoracic Society
BT- bronchial thermoplasty
ERS- European Respiratory Society
FDA- Food and Drug Administration
FVC- forced vital capacity
GERD- gastroesophageal reflux disease
GINA- Global Initiative for Asthma
ICS- inhaled corticosteroid
LABA- long-acting β agonist
LAMA- long-acting antimuscarinic agent
LTRA- leukotriene receptor antagonist

hospitalizations despite step-up asthma controller therapy including high-dose inhaled corticosteroids (ICSs) and every-other-day long-term oral corticosteroids. Comorbidities include gastroesophageal reflux disease (GERD), allergic rhinitis, chronic otitis media, and restless leg syndrome. Previous workup was positive for sensitization to multiple aeroallergens, but otherwise negative (see [Table I](#)). Medications included daily high-dose ICS and long-acting β agonist (LABA), oral leukotriene receptor antagonist (LTRA), inhaled long-acting antimuscarinic agent (LAMA), oral antihistamine, and inhaled nasal steroids as well as every-other-day oral steroids in addition to as-needed short-acting β agonists. Despite this regimen and home delivery pharmacy to ensure access to medications, JG continued to have symptoms, moderate airflow limitation on spirometry, and health care utilization. He was treated with omalizumab (Xolair, Genetech, San Francisco, Calif) and immunotherapy for 5 months before these were discontinued because of poor clinical response. On 2 occasions, he was unable to receive omalizumab because of active wheezing at the time of his visit. Spirometry has consistently shown FEV₁ 50% to 60% of predicted values with markedly positive bronchodilator response (20%–45%). Because of ongoing frequent exacerbations requiring systemic corticosteroid treatment and/or health care utilization, JG was started on mepolizumab (Nucala, GlaxoSmithKline, Research Triangle Park, NC) 13 months into every-other-day oral steroids. Since the initiation of mepolizumab, JG has not had any health care utilization. Lung function remains impaired with FEV₁ 50% to 60% predicted. JG remains on every-other-day oral prednisone (20 mg).

CASE 2

ES is a 12-year-old Hispanic male referred to a severe asthma clinic for steroid-dependent asthma, diagnosed with asthma between age 2 and 3 years. Before referral, ES had been hospitalized 7 times and had had 20 emergency department visits for asthma. Comorbidities included allergic rhinitis, GERD, and mood disorders related to poor asthma symptom control. ES had significant impairment in his quality of life including more than a month of school absences and inability to participate in football. This impairment extended to his family because his mother had missed more than a month at work and his family had given up their dog in an attempt to better control his exposure to indoor allergens. ES was a poor perceiver of symptoms until very sick; he felt well despite significant airflow limitation with FEV₁ 50% to 70% predicted and FEV₁/forced vital capacity (FVC) ranging between 50 and 70 while reporting normal Asthma Control Test (ACT) scores. Previous

workup is presented in [Table I](#). ES had been on daily prednisone for 7 months (dose was 60 mg orally for a month) before the initial site evaluation and he had gained significant weight over the previous year with a body mass index in the 98th to 99th percentile for age. ES was kept on high-dose ICS, LABA, and LAMA, and chronic oral azithromycin thrice weekly and oral LTRA were added to decrease his oral corticosteroid dose. To treat his comorbidities (allergic rhinitis and GERD), he was recommended to use an oral antihistamine, oral proton pump inhibitor, and inhaled nasal steroids. ES needed intense preexercise treatment with inhaled cromolyn, albuterol, and ipratropium. As per step 6 in the National Asthma Education and Prevention Program clinical guidelines treatment, he was started on omalizumab (every 2 weeks) because of frequent health care utilization, impaired lung function, and symptoms. ES has now been on omalizumab for the past 3 years with excellent response. He has not been hospitalized, has not missed school, or has not needed systemic steroids in the past year. He is participating in competitive football. His chronic medications have been deescalated to only a daily ICS/LABA. His most recent lung function was improved (FEV₁ 92% predicted, FEV₁/FVC 73).

CASE 3

MC is a 17-year-old white female with uncontrolled asthma who presented to a severe asthma clinic with a history of monthly exacerbations requiring systemic steroids and exercise intolerance. Comorbidities included GERD (refractory to medical therapy, underwent Nissen fundoplication), allergic rhinitis, atopic dermatitis, chronic headaches, 3 episodes of pneumonia versus atelectasis, and mild anxiety disorder. MC was not able to participate in any kind of physical activity because of her respiratory symptoms and was home-schooled. She moved out of their rural home to be close to a major academic pediatric hospital facility with asthma specialists and also away from the family dogs. Her ACT score was initially 9. Medications included 2 inhaled high-dose ICSs (1 with small particle formulation), inhaled LABA and LAMA, and chronic oral azithromycin thrice weekly. She has remained on nasal allergy treatments, oral antihistamine, sertraline, and vitamin D daily. On omalizumab, she reported improvement of rhinitis symptoms but required 3 emergency department visits for asthma where she was given corticosteroid injections and was even hospitalized a couple of times. Previous workup is presented in [Table I](#). Exercise challenge with laryngoscopy demonstrated both bronchoconstriction and mild inspiratory glottic adduction, and moderate inspiratory arytenoid prolapse during high-intensity exercise. Because of daily symptoms of chest tightness, wheezing, and cough as well as frequent exacerbations requiring systemic corticosteroids, MC was tried on mepolizumab for 5 months, but this was discontinued because of poor response (3 courses of systemic corticosteroid bursts, a decline in lung function from baseline FEV₁ 100% predicted to 70% predicted, and eventual need for chronic daily oral prednisolone therapy [15 mg]). MC now has adverse steroid side effects including Cushingoid features, weight gain, acne, hypertension, hair loss, deconditioning, and weakness without any noticeable variance or irregularity in her menstrual cycles.

DISCUSSION

Psychosocial aspects of adolescent asthma

Severe asthma in adolescence has some unique elements compared with the features of severe asthma a medical provider

TABLE I. Diagnostic workup for the cases with severe persistent asthma

Study/test	JG	ES	MC
Eosinophils	6%; absolute 550 cells/ μ L	2.6%; absolute 200 cells/ μ L	3%; absolute 200 cells/ μ L
Total serum IgE	Normal (66 IU/mL)	Elevated (1021 IU/mL)	Elevated (576 IU/mL)
Aeroallergen testing (local)	Positive to tree pollens, dust mites, and molds	Positive to tree and grass pollens, weeds, animal dander, dust mites, and molds	Positive to tree pollens, weeds, and animal dander
ABPA screen	NA	<i>Aspergillus fumigatus</i> IgE 24 IU/mL; <i>A fumigatus</i> IgG <3 IU/mL	<i>A fumigatus</i> IgE <0.35 IU/mL; <i>A fumigatus</i> IgG 27.7 mg/L (normal, 0-74)
Exhaled nitric oxide	19 ppb	24-46 ppb	11-28 ppb
Flexible bronchoscopy	Mild laryngomalacia, mild bronchomalacia	Mild edema of left upper lobe and right lower lobe bronchi	Right upper lobe scarring with widely patent bronchi
Bronchoalveolar lavage	16% neutrophils, 0% eosinophils Cultures: negative for bacteria or fungi	1% neutrophils, 0% eosinophils Cultures: negative for bacteria/fungi/mycobacteria PCR: negative for viruses, <i>Mycoplasma</i> , <i>Chlamydia</i>	2% neutrophils, 0%-1% eosinophils Cultures: negative for bacteria/fungi/mycobacteria PCR: negative for viruses, <i>Mycoplasma</i> , <i>Chlamydia</i>
Endobronchial biopsy	NA	Right lung, lower lobe: a thickened subbasal lamina that measures approximately 12 μ m; mild to moderate submucosal lymphocytic inflammation admixed with eosinophils (peak 25/hpf). CD117 shows scattered mast cells (peak 15/hpf). Neutrophils are not present. No granulomas are identified. Moderate smooth muscle hyperplasia is present. Elastotic changes are not identified.	NA
Computed tomography of sinuses	Mild paranasal sinus disease	NA	Minimal ethmoid and maxillary sinus opacification
Echocardiogram	Normal	Normal	NA
Upper gastrointestinal series	NA	NA	Normal
Esophageal impedance probe	NA	Number of episodes was above normal (while on PPI); symptom index 100%	Number of episodes was above normal (while on PPI); most are nonacidic in nature. No symptoms reported
High-resolution chest computed tomography	Patchy atelectasis and scattered areas of air-trapping; otherwise normal	Normal	Small region of subsegmental atelectasis left lower lobe; otherwise normal
Sleep study	Periodic limb movement	NA	Normal
Steroid kinetics and glucocorticoid lymphocyte stimulation sensitivity assay	NA	Rapid prednisolone clearance Relatively insensitive to fluticasone	Incomplete or delayed prednisone absorption, regular conversion to prednisolone, and a normal clearance of prednisolone; lymphocyte sensitivity to prednisolone, dexamethasone, budesonide, and fluticasone
Glycated hemoglobin A _{1c}	NA	NA	5.4%
DEXA scan	NA	Normal	Normal
Vitamin D (25-hydroxyvitamin D), total	Normal	35 ng/mL	25 ng/mL
Body box plethysmography	NA	Hyperinflation; severe airflow limitation FEV ₁ 49% reversing to 76%; FEV ₁ /FVC 0.57; FEF ₂₅₋₇₅ 23% reversing to 46%; sGaw 38% reversing to 81%	Elevated TLC, TGV, RV, and RV/TLC. Hyperinflation by TLC and air-trapping by RV/TLC; FEV ₁ 98%; FEV ₁ /FVC 0.82; FEF ₂₅₋₇₅ 85% not reversing with albuterol; sGaw 85% reversing to 129%

(continued)

TABLE 1. (Continued)

Study/test	JG	ES	MC
Exercise challenge with laryngoscopy	NA	No decline in expiratory airflow with exercise done with pretreatment. Normal anatomy with notable arytenoid erythema and edema; during exercise minimal arytenoid prolapse and normal vocal cord adduction	32% decline in FEV ₁ despite a pretreat, a warm-up in physical therapy, 2.5 mg of albuterol after the warm-up, and 4 puffs of albuterol before the test. There was moderate supraglottic edema. The vocal cords were visualized and appeared structurally normal, and there was normal symmetric movement in inspiration and exhalation at rest. During high-intensity exercise, there was mild inspiratory glottic adduction and moderate inspiratory arytenoid prolapse
Methacholine challenge	NA	NA	54% drop in FEV ₁ after 0.31 mg/mL dose; FEV ₁ PC ₂₀ <0.31 mg/mL

ABPA, Allergic bronchopulmonary aspergillosis; DEXA, dual energy x-ray absorptiometry; FEF₂₅₋₇₅, forced expiratory flow at 25%-75% of pulmonary volume; FVC, forced vital capacity; NA, not applicable; PC₂₀, provocative concentration producing a fall of 20% in FEV₁; ppb, parts per billion; PPI, proton pump inhibitor; RV, residual volume; sGaw, specific conductance; TGV, thoracic gas volume; TLC, total lung capacity.

would see in younger children or adults. Dealing with adolescence itself is a challenging phase in a child's life and compounding this phase of life with a severe chronic illness, such as asthma that can carry other comorbidities, makes management even more difficult.

Severe asthma is associated with increases in psychological distress and life stress and decreases in quality of life. This takes a toll on overall health and creates obstacles for adherence with treatment and lifestyle recommendations, further contributing to asthma severity in a vicious negative cycle.¹⁻⁴ A range of environmental, psychosocial, behavioral, and lifestyle risk factors have an impact on asthma control, with complex interactions and bidirectional relationships.¹⁻⁴ Adolescents with severe asthma report experiencing reduced quality of life secondary to not being able to have overnight visits with friends, missing considerable school time because of being sick, teasing from peers regarding their illness, and needing to severely limit or cease involvement in sports, resulting in reduced physical activity.^{1,5} Many adolescents with severe asthma have insufficient sleep, have poor sleep hygiene, and experience clinically significant insomnia.⁶ Adolescents with asthma who also suffer from another chronic medical condition such as sickle cell anemia, diabetes, arthritis, or hypertension have increased asthma symptoms, missed school days, and all-cause emergency department visits than those without other chronic medical conditions.⁷ The use of oral corticosteroids, such as prednisone, is associated with the side effects of anxiety and depression, with higher doses being related to more intense symptoms in children.⁸ Most research studies suggest that children with asthma display more behavioral and emotional difficulties than do their healthy peers, with significant increases as the severity of asthma increases.⁹ These psychological difficulties, in turn, are associated with increased functional limitations,¹⁰ poorer asthma management,¹¹ and higher rates of treatment nonadherence.¹² Medication nonadherence is a significant concern with children and adolescents.¹³ This nonadherence can be intentional or unintentional. Examples of

unintentional factors include improper technique,¹⁴ a lack of understanding regarding asthma and asthma management, limited symptom recognition,¹⁵ issues in family functioning,¹⁶ forgetting,¹⁷ and child psychological distress.¹² Examples of intentional factors include concerns about controller medications (eg, side effects and cost)¹⁸ and beliefs that medications will not be helpful.¹⁷ Improved asthma medication adherence, and consequent improved asthma control, can lead to reduced asthma morbidity and mortality and increased quality of life.^{15,19,20} Investigations have shown that providing education about asthma and asthma medications, combined with an incorporation of psychosocial interventions (such as behavioral or cognitive-behavioral interventions), resulted in improved asthma medication adherence,²¹ reduced asthma severity,²² and reduced child psychological problems.²³

ES and MC have developed side effects from corticosteroids, including weight gain and mood/emotional changes, which are also likely related to decreased physical inactivity and reduced coping outlets because of not being able to play sports that they used to enjoy. ES has a history of sadness and anxiety about possible death from asthma and had thoughts of self-injury at a time when he was feeling particularly sad about his asthma. MC describes that she has nightmares about not being able to breathe, feels like she is "living like a 60-year-old" because of her limited lifestyle secondary to her asthma, and often feels angry after time with her friends because they are "full of life and I'm so tired." As these patients are transitioning to adulthood, they are struggling with how to pursue their academic and personal goals given limitations associated with their asthma. In addition, their families have experienced concerns about their health and stressors of financial concerns regarding the cost of treatment. In extreme cases like MC's, she has experienced separation from her family before college so she can be managed in a specialty center. Educating adolescents and getting them motivated can take some creative scheme. Poor perception of impaired lung function is one of these educational challenges with adolescents, which was

TABLE II. FDA-approved biologics for adolescents with severe asthma

Name	Omalizumab (Xolair)	Mepolizumab (Nucala)	Benralizumab (Fasenra)
Mechanism of action	Recombinant humanized IgG ₁ anti-IgE mAb	Humanized anti-IL-5 mAb	Humanized anti-IL-5 receptor (alpha subunit) mAb
Ages approved	6 y and older	12 y and older	12 y and older
Indications	Moderate to severe asthma with at least 1 perennial aeroallergen and an elevated serum IgE level	Eosinophilic asthma	Severe asthma in those aged 12 y and older, and with an eosinophilic phenotype
Dosing regimen	Subcutaneous every 2-4 wk	Subcutaneous every 4 wk	Subcutaneous every 4 wk for the first 3 doses, followed by once every 8 wk
Predictors of success	Allergic asthma, fall exacerbations (seasonal), high-dose ICSs, frequent exacerbations, inner-city children/adolescents	Eosinophilia, daily oral steroids	Elevated blood eosinophil levels, daily oral steroids

TABLE III. Potential future therapies for adolescents with severe asthma

Name	Reslizumab	Dupilumab	BT
Mechanism of action	mAb to IL-5	mAb to IL-4 receptor that blocks IL-4 and IL-13 signaling	Radiofrequency thermal treatment of airway smooth muscle on 3 separate occasions 3 wk apart
Ages approved	18 y and older	Not yet approved	18 y and older
Indications	Severe asthma, T _H 2 inflammation	Severe asthma, T _H 2 inflammation	Severe persistent asthma, not well controlled on ICS/LABA, patients who do not qualify for or respond to anti-IgE therapy
Predictors of success	≥400 eosinophils/μL	Unclear as of yet; tested in patients on medium- to high-dose ICSs with LABA	Unclear as of yet; multisite investigations ongoing
Positive effects	Reduced symptoms and exacerbations, improved FEV ₁	Improved FEV ₁ and reduced exacerbations	Improvement in quality of life, decreased rate of exacerbations
Adverse effects	Oropharyngeal pain, anaphylaxis (rare)	Temporarily increased blood eosinophils	Transient worsening of asthma; long-term efficacy and safety unknown

especially true for ES who had limited symptom perception and did not regard himself to be a high-risk patient at all. These psychosocial issues can also create barriers for compliance with treatment. Given this pattern, it is strongly recommended for providers working with adolescents with severe asthma to consider the psychological impact of asthma and how this, in turn, can contribute to asthma severity and morbidity. Addressing psychological adjustment and functioning in this age group, lifestyle factors, and family stress is essential for working with an adolescent patient and his or her family toward adherence with treatment recommendations and improvements in overall health.¹

Diagnosis of severe asthma in adolescents

There are certain unique developmental aspects of asthma in adolescence that are worth noting: effect on lung function, heterogeneity, immunologic phenotypic characteristics, and treatment response. Adolescence, especially postpubertal, is the phase when lung growth can take off and reach its near maximum.²⁴⁻²⁷ It is not uncommon to see no lung function impairment, exemplified by MC, or even “supernormal” lung function in adolescents who have severe asthma meeting most other criteria, yet there are patients who already have reduced lung growth, or have reached their maximum lung growth prematurely. Airway obstruction (for MC) was suggested by findings of hyperinflation from body box plethysmography (Table I), and the diagnosis of asthma was confirmed by exquisite bronchial

hyperresponsiveness from bronchoprovocation challenges (exercise and methacholine). Airflow limitation meeting the modified Global Initiative for Chronic Obstructive Lung Disease spirometric criterion of a postbronchodilator FEV₁/FVC ratio below the lower limit of the normal range was found in 36% of patients with reduced lung growth followed in the Childhood Asthma Management Program cohort by age 23 years.²⁵ Various patterns of lung function are evident in these adolescents: JG continues to have airflow limitation (although with improved symptom control), ES had low lung function initially and has since improved, and MC who started with normal lung function (yet significant symptom burden) has since had lung function decline over the past year.

These 3 cases demonstrate the different faces of severe asthma. JG has frequent symptoms and low lung function, ES has minimal reported symptoms and low lung function, and MC has significant impairment, yet normal lung function. The common feature is the presence of frequent exacerbations. They all meet the definition for severe asthma defined by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) as asthma that requires treatment with high-dose ICSs (defined by age) and a long-acting bronchodilator or leukotriene modifier/theophylline (second controller) for the previous year or systemic corticosteroids for more than 50% of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy.²⁸ Furthermore, “uncontrolled” asthma is defined as at least 1 of the following:

1. *Poor symptom control*: Asthma Control Questionnaire score consistently higher than 1.5, ACT score less than 20 (or “not well controlled”) by the National Asthma Education and Prevention Program/Global Initiative for Asthma (GINA) guidelines;
2. *Frequent severe exacerbations*: 2 or more bursts of systemic corticosteroids (>3 days each) in the previous year;
3. *Serious exacerbations*: at least 1 hospitalization, intensive care unit stay, or mechanical ventilator in the previous year;
4. *Airflow limitation*: after appropriate bronchodilator with FEV₁ less than 80% predicted.

It is worth mentioning that the current ERS/ATS definition does not address those children and adults who are not on controller medications, yet meet the criteria for uncontrolled asthma. *Severe therapy-resistant asthma* is defined as asthma that is difficult to control even after confirming the diagnosis and managing comorbidities, adherence, or environmental factors,^{29,30} whereas *difficult-to-treat asthma* is defined as poor control of asthma in the presence of continued symptomatic comorbidities, poor adherence, and environmental trigger exposures. In light of this, it is important to realize that it is not necessary for patients to meet the definition of “severe asthma” (by any guideline, agency, task force, etc) to have “difficult to control” asthma. Our patients meet any of these definitions, and the status or severity of their asthma is not questionable. In some cases, despite aggressive management of their comorbidities (such as in the cases of MC and ES, eg, Nissen fundoplication for uncontrolled GERD in MC, aggressive preexercise treatment, and eliminating environmental triggers), asthma is still poorly controlled. These patients had measures to maximize adherence to medications and had close supervision by their parents. The natural history, risk factors, evaluation, and treatment of severe asthma in children and adolescents have been covered extensively by guideline and consensus committees and recent reviews.^{28,29,31–39} The evaluation of these adolescents at 2 specialized centers, Cincinnati Children’s Hospital Medical Center and National Jewish Health, has been extensive (Table I), consistent with these guidelines.

Treatment of severe asthma in adolescents

The treatment recommendations for adolescents reflected in national and international guidelines are similar to those for adults, but different for younger children.^{28,29,33,34} Adolescents and adults with severe asthma should be treated with high-dose ICSs or oral corticosteroids combined with LABA and other add-on therapies, such as LTRA, LAMA, or theophylline.^{1,28,29,33,34} There are different cutoffs for high-dose ICSs for adolescents and adults compared with children younger than 12 years.^{28,33} Because of side effects, regular monitoring for children with severe asthma who have exposure to frequent/continual oral corticosteroids or high doses of ICSs is recommended.^{28,29} This may include bone density testing, ophthalmologic examination, testing of adrenal function, and/or consultation with a pediatric endocrinologist. ICS use in children has been shown to lead to a small reduction in adult height.⁴⁰ There remains concern about an increased risk of adrenal suppression and growth suppression with high doses of ICSs (compared with low- or medium-dose ICSs); however, adult studies have shown that patients with asthma do not absorb ICSs as well as healthy controls.^{28,41,42} It is thought that the lower absorption of ICSs seen in patients with

asthma is due to airway inflammation and therefore higher doses of ICSs may be appropriate.²⁹ Although the data are limited, it has been shown that treating children with severe asthma with higher doses of ICSs can lead to lower oral corticosteroid doses.⁴³ There has been some debate over the utility of small particle size ICSs in patients with severe asthma, both adult and children, with some studies showing conflicting results; however, meta-analyses of randomized controlled trials have not demonstrated differences in asthma outcomes between different particle size ICSs.^{44–52} LABAs, combined with ICSs, are medications that have been shown to improve asthma outcomes compared with higher doses of ICSs or addition of an LTRA in children and adolescents who remain uncontrolled on low-dose ICSs.³³ Despite early concerns about LABA safety,^{53–55} recent studies, including the VESTRI⁵⁶ and AUSTRI^{56–58} trials, have demonstrated their safety and efficacy when adding LABAs to ICSs.^{59–64} LTRAs are included in guideline-based therapies and have been shown to be effective in some children, although the patient characteristics that indicate responsiveness are not well defined.^{28,62} Methylxanthines remain a guideline-based treatment option; however, they are infrequently used because of their safety profile and narrow therapeutic window as well as limited data demonstrating efficacy over other therapies.^{28,33,34,65} Another long-acting bronchodilator that has been approved by the Food and Drug Administration (FDA) for children 6 years and older with moderate to severe asthma is tiotropium, a LAMA. When added to ICS therapy in patients with moderate to severe asthma, tiotropium has been shown to improve lung function and decrease asthma symptoms.⁶⁶ For patients with poorly controlled severe asthma, addition of tiotropium to a combination ICS/LABA regimen improved lung function and reduced the need for oral corticosteroids.⁶⁷ Younger adults with lower lung function, higher degrees of bronchodilator reversibility, and higher cholinergic tone (ie, lower resting heart rate) may have the most benefit from tiotropium when added to ICSs.^{68,69} GINA 2017 recommends add-on tiotropium in patients 12 years and older with a history of exacerbations despite step 4 treatment.³³

Stepwise approach for this adolescent age group on the basis of control or severity is primarily based on escalation of ICS dose. There is no head-to-head comparison of these adjuvant controller therapies (small particle size ICSs, LABA, theophylline, LTRA, and LAMA) for children or adolescents with severe asthma. There is a growing paradigm shift toward personalized medicine for patients with severe asthma.⁷⁰ It is still uncertain what patient characteristics indicate responsiveness to any of these in severe asthma. Quite often, specialists get caught up with eventually using most or all of them. These patients and their families may already be struggling in many aspects of their life, including having to pay for and take a number of medications.

Phenotype-directed therapies for severe asthma in adolescents

Advances in diagnostic phenotyping and endotyping for patients with severe asthma could lead to earlier and simpler effective treatment plans.^{70–77} All 3 of our adolescent patients have evidence of aeroallergen sensitization on the basis of skin testing (ES and MC having elevated serum IgE), eosinophilia (especially so in JG), and modest elevation in exhaled nitric oxide (albeit on systemic and high-dose ICSs), suggestive of T2 inflammation. Serum periostin is a biomarker that has been

found (primarily in adults) to be reflective of T2 high inflammatory response; however, it may have limited utility in adolescents in whom variability is more pronounced because of growth and development.⁷⁸⁻⁸¹ The utility of periostin in personalized medicine for children and adolescents with severe asthma remains unclear.⁸²⁻⁸⁴ JG was tried on aeroallergen immunotherapy without success. Specific allergen immunotherapy has been shown to improve symptom control, medication use, and airway reactivity in children with mild to moderate asthma; however, most of these studies evaluated single-allergen immunotherapy, whereas many patients with severe asthma have polysensitization to aeroallergens, and allergen immunotherapy has not been evaluated in children with severe asthma.^{71,72} The process of escalating immunotherapy doses in adolescents with severe asthma who are often sick and unstable is challenging. Biologics currently available target T2 inflammation.^{29,71,73,76} At present there are 3 FDA-approved biologics for adolescents with severe asthma, as presented in Table II. Omalizumab is a recombinant humanized IgG₁ anti-IgE mAb that is injected every 2 to 4 weeks in patients with chronic allergic asthma with an elevated serum IgE level (30-700 IU/mL for adolescents; 30-1300 IU/mL for children aged 6-11 years) and evidence of sensitization to at least 1 perennial aeroallergen.⁸⁵⁻⁹⁰ It is approved for use in children 6 years and older.⁸⁵ Omalizumab significantly reduces the rate of asthma exacerbations, severe exacerbations, and emergency department visits for teenagers and adults with poorly controlled severe persistent asthma.⁸⁷ Furthermore, in a study of inner-city children and young adults with allergic sensitivity and asthma requiring high-dose ICSs and experiencing frequent exacerbations, addition of omalizumab led to improved asthma control, a reduction in seasonal peaks in exacerbations, and a reduction in the need for additional medications to control asthma.⁸⁶ These outcomes occurred in the context of reductions in doses of ICSs and LABAs. Omalizumab may be most effective for patients who require high-dose ICSs and experience frequent exacerbations.^{91,92} Challenges of omalizumab therapy include body weight restrictions, serum IgE level requirements, and cost of treatment that impacts insurance approval.⁹³⁻⁹⁵ Of our 3 patients tried on omalizumab, only ES responded successfully in terms of asthma outcome and lung function. A second biologic therapy is mepolizumab and it is approved for children 12 years or older for the treatment of eosinophilic asthma.⁹⁶ It is a subcutaneous injectable (100 mg every 4 weeks) humanized mAb directed against IL-5. Mepolizumab has been shown to modestly increase FEV₁, reduce exacerbations associated with emergency room visits and hospitalizations, and improve asthma control and symptoms.⁹⁶⁻⁹⁸ Mepolizumab has also been shown to have a significant corticosteroid-sparing effect.⁹⁶ Since starting mepolizumab, JG has demonstrated reduced exacerbations and symptoms, although lung function to date has not changed. It is hoped that in time, lung function will also improve. The blood eosinophil count appears to predict response to mepolizumab^{97,98} and that was true for JG (peripheral blood eosinophils, 6%; absolute, 550 cells/ μ L). A third biologic therapy is benralizumab (Fasenra, Astrazeneca, Gaithersburg, Md) and it was recently (November 2017) approved by the FDA for add-on maintenance treatment of patients 12 years and older with severe asthma, and with an eosinophilic phenotype.⁹⁹ It is a subcutaneous injectable (30 mg every 4 weeks for the first 3 doses, and 30 mg every 8 weeks thereafter) humanized mAb directed

against the alpha subunit of the IL-5 receptor.^{99,100} Benralizumab has been shown to reduce oral glucocorticoid needs and exacerbation rates for these patients.⁹⁹⁻¹⁰⁴ MC did not have a good response to either omalizumab or mepolizumab therapy. It is still unclear as to how to identify responders from non-responders and which biologic therapy would be most beneficial for a patient who meets eligibility for multiple therapies. Reslizumab, similar to mepolizumab, is an anti-IL-5 mAb that has been approved in adults (patients 18 years and older) with asthma and eosinophilia (≥ 400 cells/ μ L) after demonstrating improved lung function, asthma control and symptoms, and quality of life.^{105,106} The advantage it offers for adults, although given intravenously, is being able to adjust dosage on the basis of weight.

Potential therapies for adolescents with severe asthma

Over the past decade, new targeted therapies have been developed for patients with severe asthma, on the basis of phenotypic and potential endotypic characteristics.^{31,70,85,92} Commonly, therapies for asthma are evaluated for safety and efficacy and then approved by regulatory agencies (FDA, European Medicines Agency, and Therapeutic Goods Administration) for use in adults before use in pediatrics (see Table III for some emerging therapies). Dupilumab is a fully human mAb to the alpha subunit of the IL-4 receptor that blocks both IL-4 and IL-13 signaling. Dupilumab has shown a 60% to 80% reduction in exacerbations and an increase in FEV₁ in patients with asthma treated with medium- or high-dose ICSs and LABAs regardless of blood eosinophil count.¹⁰⁷ However, it is currently FDA-approved only for the treatment of moderate to severe atopic dermatitis in patients 18 years or older. There are a number of other immunomodulatory mAbs being investigated, predominantly focusing on the T_H2 inflammatory cascade.^{29,71-73} Biologics undergoing current development and investigational trials include tezepelumab (targeting thymic stromal lymphopoietin that regulates type 2 inflammation through activity on dendritic cells, T and B cells, and innate immune cells),¹⁰⁸ imatinib (targeting KIT receptor on mast cells),^{73,109} tralokinumab (targeting IL-13),^{110,111} and lebrikizumab (targeting IL-13).^{72,73,112-115}

There have been limited investigations into T2-low inflammation phenotype (typically neutrophilic predominant inflammation). Neutrophils release proteases, reactive oxygen species, and inflammatory mediators, which may exacerbate asthma symptoms and be poorly responsive to corticosteroids.¹¹⁶ It is postulated that reducing neutrophilic inflammation might provide clinical benefit to select patients with asthma as well as patients with chronic obstructive pulmonary disease, although this approach raises concern about reducing the protective role of neutrophils in innate host immunity and whether this would increase the risk of lung infections.^{116,117} Chronic macrolide therapy is often used for antineutrophilic anti-inflammatory effect in cystic fibrosis¹¹⁸ and has been suggested for the treatment of childhood asthma associated with persistent neutrophilic inflammation.¹¹⁹ An attempt by the Childhood Asthma and Research Education Network to study the steroid-tapering effects of chronic macrolide therapy and montelukast in children with moderate to severe asthma met challenging issues primarily related to meeting required sample size, yet futility analyses revealed that neither drug was effective with respect to the

ICS-tapering effect.¹²⁰ Both ES and MC have been tried on chronic macrolide therapy as well. Chronic infections can contribute to severe asthma and there is adult literature showing that *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are associated with lower lung function and bronchial hyperreactivity that improve with macrolide therapy.^{29,121,122} It should be stressed that current practice guidelines (ATS/ERS/GINA) recommend against macrolide therapies.^{28,33,34} Considerations and investigations into T2-low inflammation in severe asthma are underway and include focusing on anti-TNF, CXCR2, CXCL1, CXCL8, IL-17, IL-23, IL-1, IL-6, and innate T cells as targets of therapies.¹¹⁶ A selective CXCR2 receptor antagonist, SCH57123, has demonstrated a reduction in sputum neutrophils, fewer exacerbations, and a trend toward improvement in Asthma Control Questionnaire score in a small study of adults with severe asthma.¹²³ At this time, there are no recommended neutrophil-targeted therapies for severe asthma in children and adolescents, although this is an area of ongoing research.¹¹⁶

Bronchial thermoplasty (BT), a radiofrequency thermal treatment of the airways of patients with severe asthma, has demonstrated long-term effectiveness and safety in adults with severe uncontrolled asthma using step 5 of the US asthma guideline treatment.³⁴ Applied over the course of 3 bronchoscopic treatments, this innovative procedure has been shown to reduce severe exacerbations by one-third and reduce emergency department visits by 85%, with a benefit that persists up to 5 years.^{124,125} Several studies have now demonstrated that BT reduces airway smooth muscle, nerve cell receptors, and proremodeling mediators.¹²⁶⁻¹²⁸ Despite this disease-modifying effect, BT, which is approved for those 18 years and older, has yet to be studied in adolescents, and guidelines suggest that the procedure be limited to trials or registries.^{71,73}

CONCLUSIONS

Detailed descriptions of 3 adolescents with severe asthma speak of the heterogeneity of severe asthma. There are unique aspects adolescents present with and the approach and management of this chronic and debilitating illness in this age group should be tailored. A multidisciplinary approach (ie, allergy, pulmonology, social work, psychology, asthma educator, etc) is necessary. Specific focus on psychological issues, home environment, adherence, education, home delivery of medications, and school administration of medications can be paramount in improving the care of children and adolescents with asthma. There are physiologic and biologic changes that can have an impact on disease phenotyping and monitoring of treatment response. There are adolescents who have standard therapy-resistant asthma, despite managing their comorbidities, who respond to biologic therapy. Yet, there are also adolescents who remain refractory despite currently available biologic therapy. Therapies available for adults may be beneficial for these patients. Investigation into this and exploring predictors of specific treatment response using phenotypes are needed to provide better care to these challenging patients.

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