The Tempest: Difficult to Control Asthma in Adolescence

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INFORMATION FOR CATEGORY 1 CME CREDIT

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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.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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 FEV_1 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 FEV_1 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 FEV_1 50% to 70% predicted and FEV_1/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 (FEV_1 92% predicted, FEV_1/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 FEV_1 100% 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