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Asthma: Overdiagnosed, Underdiagnosed, and Ineffectively Treated

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Asthma is a complex, inflammatory condition characterized by airway obstruction, bronchial hyperresponsiveness, maladaptive dynamic hyperinflation, a disconnect between pulmonary physiology and symptom recognition, comorbidities, multiple triggers, and with undue susceptibility to viral infections. Many patients do not achieve control. Decision making can be difficult for physicians and health care professionals because there are heterogeneous responses to pharmacotherapy, immunotherapy, and biologic treatments. According to Centers for Disease Control (CDC) data for 2015, the prevalence of current asthma in the United States is 7.8% (children/adolescents < 18 years of age = 8.4%; adults ≥ 18 years = 7.6%).¹ Categorized by race/ethnicity, the findings are familiar: white non-Hispanic = 7.8%, black non-Hispanic = 10.3%; other non-Hispanic = 6.9%; Hispanic = 6.6%, with differences between Puerto Rican = 13.7% and Mexican/Mexican/American = 6%.¹ The asthma death rate of 3,615 people for the year 2015 is approximately 1.1/100,000 population with a burden 3-fold higher in black non-Hispanics than either in white non-Hispanics or Hispanics.¹ The data for 2015 confirm earlier, similar findings that 46.9% of patients with current asthma had experienced 1 or more “asthma attacks” in the past 12 months.¹ The focus of this issue of *JACI: In Practice* is an across the spectrum of life perspective on asthma with the hope of providing relevant new insights and improving care for patients.

Whether an individual is diagnosed with asthma as a baby, school-aged child, adolescent, or adult, it is important to be aware of overdiagnosis, underdiagnosis, and undertreatment. Because asthma diagnoses are frequently made on the basis of symptoms without objective measurements of variable airflow obstruction or bronchial hyperresponsiveness, misdiagnosis is possible.² Obese patients are more likely to report dyspnea and asthma-like symptoms compared with nonobese patients; thus, obese patients could be overdiagnosed with asthma.³ As high as 30% of physician-diagnosed asthma based on symptoms may not be asthma after measuring pulmonary function testing.² Furthermore, asthma in older adults is often underdiagnosed because older adults may be misdiagnosed with chronic obstructive

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pulmonary disease (COPD) rather than asthma; this underdiagnosis can lead to undertreatment. In The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (Tenor II) longitudinal study of patients with severe or difficult-to-treat asthma, 25.8% of patients had experienced exacerbations requiring oral steroids or hospital treatment in the previous 3 months, and undertreatment with medications was observed in this study.⁴ Undertreatment of asthma also occurs as many providers do not implement national guidelines for the treatment of asthma.⁵ In addition, undertreatment of asthma can occur due to patients not taking asthma medications because they are worried about potential adverse effects or they do not understand the need for controller medications when they feel well.⁶ Cost considerations with inhaled corticosteroid (ICS) and ICS/long-acting beta-agonist (LABA) products may result in patients using less than prescribed amounts as well.

The review by Lee-Sarwar and Litonjua⁷ in this issue provides a summary of the literature of the effect of diet during pregnancy on risk of childhood asthma by reviewing nutritional intervention trials, meta-analyses, and observational studies. Multiple studies suggest that vitamin D supplementation may have a protective effect on the development of childhood asthma, although the dose of vitamin D required for prevention has not been established. The pathophysiologic mechanisms involved include evidence that vitamin D promotes the innate antimicrobial responses and promotes regulatory T-cell differentiation and IL-10 production; vitamin D deficiency is also associated with increased airway smooth muscle mass and hyperresponsiveness. Moreover, high-dose omega-3 polyunsaturated fatty acids were associated with a reduction in risk of persistent wheeze or asthma in 1 clinical trial, although other trials have not supported these findings. Proposed mechanisms for the relationship of omega-3 polyunsaturated fatty acids and asthma include that increased dietary omega-3 fatty acids could displace arachidonic acid, a precursor for inflammatory and anti-inflammatory lipid mediators, leading to the development of asthma. Furthermore, maternal dietary vitamin E intake during pregnancy has been associated with decreased asthma in offspring, possibly by decreasing pulmonary inflammation. Other reviewed studies suggest that vitamin C supplementation in smoking pregnant women may prevent wheezing in children, and selenium supplementation may prevent asthma or wheeze in offspring with certain genetic variants.

The clinical management review by Naja et al⁶ focuses on asthma in school-aged children and encompasses racial/ethnic and socioeconomic disparities, environmental exposures, current treatment guidelines, and novel therapeutics. In the United States, Puerto Rican American and African Americans carry a disproportionate burden of asthma morbidity. Children from economically disadvantaged neighborhoods also have higher rates of asthma incidence and worse asthma morbidity due to stress, substandard housing, lack of social support, and other factors. Targeting the indoor environment is likely to be important in decreasing asthma morbidity. Specifically, limiting exposure to indoor pollutants, such as dust mites, rodents, cockroach and pet allergens, secondhand smoke, and nitrogen dioxide, may help improve asthma control and lung function. Another environment for interventions is the school, as children spend a large portion of the day in schools and daycare centers. Studies have shown that cockroach and mouse allergens are highly prevalent in inner-city school classrooms. Furthermore, schools are frequently located close to highways and heavy traffic routes where exposure to traffic pollution can negatively affect the indoor quality of

schools. Despite asthma guidelines that address the management of asthma and the availability of many efficacious asthma medications, many children with asthma continue to suffer symptoms. The newest class of medications, biologics, include omalizumab, which is now approved for children 6 years and older with moderate-to-severe asthma, and mepolizumab and benralizumab, which are approved for use in children 12 years or older for eosinophilic asthma. Reslizumab is approved for patients 18 years and older. As additional biologics become approved for clinical use, clinical trials in pediatric populations will be important. The authors conclude that decreasing asthma morbidity in school-aged children will require minimizing harmful environmental exposures, understanding the role of racial/ethnic and socioeconomic disparities, and clinical trials to assess novel therapeutics.⁶

In a Grand Rounds Review, Burg et al explore the real-world challenges for adolescents with persistent asthma including when asthma becomes much more difficult to manage.⁸ How can self-efficacy (effective self-management) be achieved or at least approached for better control of the adolescent's asthma? Can we have shared values with the patient regarding initiating the action plan? Identification of comorbidities and the priorities of the adolescent regarding asthma management continue to be targets of the allergist-immunologist or other asthma specialist.

The therapeutic benefits of treatments for asthma may be reduced in patients over the age of 65 years, and comorbidities including cardiac conditions, sleep apnea, obesity, and COPD may complicate diagnosis and treatment in this age group. Because product labeling does not list ages 66 years and more for biologics or sublingual immunotherapy, the physician and health care professional can be hampered when advocating for their elderly patients who are either receiving these treatments and reach 66 years of age or who would likely be a good responder to them. Baptist and Busse⁹ review many aspects of this topic of asthma in patients over the age of 65 years.

Inhaled corticosteroids for persistent asthma have been available for over 40 years in the United States and longer in other countries. Many, but not all, children and adults respond well, and inhaled corticosteroids have an excellent safety profile in recommended dosages. When the dosages are increased further, however, the marginal increase in forced expiratory volume in 1 second or reduction of symptoms may be modest, and adverse effects such as secondary adrenal insufficiency may be measureable with low-dose (1 mcg) adrenocorticotropin stimulation of the hypothalamic pituitary adrenal axis. Heffler et al¹⁰ explore many aspects of the safety and adverse effects of inhaled corticosteroids. They even speculate on the implementation of biologic therapies for persistent asthma that would be at Step 3 or 4, according to the National Heart Lung Blood Institute National Asthma Education and Prevention Program Expert Panel Report 3 and Global Initiative for Asthma categories. If it would be safe, effective, and of reasonable cost, wouldn't it be intellectually satisfying if we could treat patients with persistent asthma with products directed more upstream? Time will tell, but inhaled corticosteroids remain our key anti-inflammatory medication currently.

Although much has been discovered about asthma and its treatment, the challenges remain. There remains no cure for bronchial hyperresponsiveness, inflammation in the airways, and

hypersecretion of bronchial mucus. Many patients are not receiving optimal treatments, and morbidity and mortality remain too high. We hope this issue will provide insights into improved care for our patients and remind us to keep reassessing the level of control and the extent of risks so that asthma is less burdensome for our patients and their families.

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