

Key Issues in Pediatric and Adult Severe Asthma: Staying Grounded as Biologics Take Us to New Heights



Theresa W. Guilbert, MD, MS^{a,b}, and Elliot Israel, MD^c Cincinnati, Ohio; and Boston, Mass

Asthma remains the most common chronic respiratory disease, affecting more than 300 million individuals worldwide and an estimated 6.8 million children in the United States.^{1,2} These individuals have significant risk for hospitalizations, emergency room visits, and school absences leading to significant social and economic burden for both families and the health care system.³ Difficult-to-treat and severe asthma account for almost half of the cost of asthma in a given year and is the theme of this issue of the *Journal*. Drugs targeting type 2 inflammation represent a breakthrough development in this area, and their use is described in both pediatric and adult medicine. Further, choosing among them is a topic of one of the articles in the issue,⁴ but as most of the articles in this issue emphasize, the approach to the difficult-to-control asthmatic still requires basic, grounded clinical assessment including assuring that asthma is the cause of symptoms and that additional issues that might be complicating asthma are addressed.

Thus, both the pediatric⁵ and the adult⁶ difficult-to-control asthma management articles within this issue make the distinction between difficult-to-treat and severe asthma. As they point out, the term difficult-to-treat asthma can be applied to a patient who remains poorly controlled despite being prescribed at least National Asthma Education and Prevention Program (NAEPP)⁷ or Global Initiative of Asthma (GINA) step 4 therapy.⁸ Only a subset of individuals with difficult-to-treat asthma have severe

asthma, which, as noted in the accompanying articles, is defined as asthma that remains difficult to treat after confirming the diagnosis and addressing issues regarding adherence⁹ and comorbidities.¹⁰ As emphasized by the authors, it is vital to use a systematic assessment process to address these latter issues, which can make asthma difficult to control.

As noted in several of the articles,^{4,6} biologic therapy addressing the contribution of type 2 inflammation has changed the face of severe asthma for those in whom type 2 inflammation contributes to their poor control. However, in part owing to the expense of such therapy (\$40,000–\$50,000/y), and the fact that perhaps one-third to one-half of patients eligible for these drugs may not have a complete response, it behooves clinicians to ascertain that these drugs are primarily being used for severe asthma, as opposed to difficult-to-treat asthma, and that they are being used in those most likely to respond. As discussed in the article on adherence and health literacy,⁷ almost half of difficult-to-treat asthma is related to poor adherence. A thorough investigation of those adherence and health literacy issues⁷ as well as exploration of exposure to irritants and allergens,^{10,11} especially ongoing smoking or second-hand smoke exposure (an issue for 10%–20% of patients), before the initiation of biologic therapy is critical.

The development of drugs that address type 2 pathobiology now almost represents an embarrassment of riches. Clinicians are frankly puzzled as how to choose among them. Pavord and colleagues⁴ have done an admirable job of trying to provide a rubric for such an approach. However, one needs to realize that information on the use of biomarkers and phenotypes is a rapidly evolving area and that a considerable degree of overlap still remains in the phenotypes that best respond to these therapies.

As pointed out by the different authors, whereas the biologics offer great possibilities for those who appear likely to respond based on biomarkers and phenotypes, 40% to 50% of patients with severe asthma are not in that category. Further, as mentioned previously, a substantial minority of patients who qualify do not have complete responses. A return to foundational principles with systematic assessment for adherence and comorbidities is doubly important in those patients. As discussed, the available options for such patients remain limited, with azithromycin probably the most promising for those who are not candidates for or do not adequately respond to biologics.

Several essential areas for exploration and research have been highlighted in this issue in order to continue the quest to improve outcomes in those with difficult-to-treat asthma. What are the synergistic or effect-modifying effects of comorbidities on response to medications and asthma outcomes? What novel biomarkers can distinguish inflammatory endotypes? Which biomarkers can be used to predict response and detect early treatment response to asthma biologics? When should a biologic therapy be discontinued

^aDepartment of Pediatrics, University of Cincinnati, Cincinnati, Ohio

^bPulmonary Division, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

^cDivisions of Medicine, Pulmonary, and Critical Care and Allergy and Immunology, Brigham & Women's Hospital, Harvard Medical School, Boston, Mass

This study received support from the Gloria M. and Anthony C. Simboli Distinguished Chair in Asthma Research.

Conflicts of interest: T. W. Guilbert reports personal fees from American Board of Pediatrics, Pediatric Pulmonary Subboard, Novartis, GSK, and TEVA; grants from NIH; grants and personal fees from Sanofi/Regeneron/Amgen and AstraZeneca; and royalties from UpToDate. E. Israel reports royalties from UpToDate; consulting fees from AB Science, Allergy and Asthma Network, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Avillion, Biometry, Cowen, Equillum, Genentech, GlaxoSmithKline, Merck, NHLBI, Novartis, Pneuma Respiratory, PPS Health, Regeneron, Sanofi Genzyme, Sienna Biopharmaceuticals, and TEVA; honoraria from Westchester Medical Center and Yale School of Medicine; payment for expert testimony from Cambridge Medical Experts, Danaher Lagnese, and SettlePou; participation on a Data Safety Monitoring Board as Chair from Novartis; and stock options from Vorso.

Received for publication December 20, 2021; accepted for publication December 20, 2021.

Corresponding author: Theresa W. Guilbert, MD, MS, Pulmonary Division, Cincinnati Children's Hospital and Medical Center, 3333 Burnet Ave., MLC 7049, Cincinnati, OH 45229. E-mail: Theresa.Guilbert@cchmc.org.

J Allergy Clin Immunol Pract 2022;10:420-1.
2213-2198

© 2021 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2021.12.015>

in favor of another one and which medication should be selected? Which evidence-based adherence interventions are the most effective for adults and children with severe or difficult-to-control asthma? What is the impact of the health literacy of patients on severe or difficult-to-control asthma outcomes?

The largest research gap remains in the development of treatments for those who do not have of significant type 2 inflammation and those who do not respond, or do not respond completely, to type 2-targeted therapy. As emphasized by the authors, staying grounded in careful assessment of adherence, obstacles to care, environmental precipitants, and comorbidities is essential for these patients while we await exciting new research that will take us to new heights in addressing the underlying pathobiology and providing new interventions for our patients.

REFERENCES

1. Centers for Disease Control and Prevention. Current Asthma and Asthma Attack Prevalence (2011–2017): United States. Accessed December 17, 2021. <https://www.cdc.gov/asthma/nhis/default.htm>
2. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breyse PN. Vital signs: asthma in children—United States, 2001–2016. *MMWR Morb Mortal Wkly Rep* 2018; 67:149-55.
3. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008–2013. *Ann Am Thorac Soc* 2018;15:348-56.
4. Pavord ID, Hanania NA, Corren J. Choosing a biologic for patients with severe asthma. *J Allergy Clin Immunol Pract* 2022;10:410-9.
5. Bush A, Fitzpatrick AM, Saglani S, Szeffler SJ. Difficult-to-treat asthma management in school-age children. *J Allergy Clin Immunol Pract* 2022;10:359-75.
6. Menzies-Gow A, Moore WC, Wechsler M E. Difficult-to-control asthma management in adults. *J Allergy Clin Immunol Pract* 2022; 10:378-84.
7. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI), administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Cloutier MM, Baptist AP, et al. 2020 focused updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol* 2020;146:1217-70.
8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention; 2021. Accessed December 17, 2021. <https://ginasthma.org/>
9. Zaeh SE, Ramsey R, Bender B, Hommel K, Mosnaim G, Rand C. The impact of adherence and health literacy on difficult-to-control asthma. *J Allergy Clin Immunol Pract* 2022;10:386-94.
10. Gaffin JM, Castro M, Bacharier LB, Fuhlbrigge A L. The role of comorbidities in difficult-to-control asthma in adults and children. *J Allergy Clin Immunol Pract* 2022;10:397-408.
11. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. *Respirology* 2017;22:651-61.