ABOUT THE AUTHOR

Jason K Lee, MD, FRCPC, FAAAAI, FACAAI

Dr Lee is a practicing physician specializing in immunotherapy treatment of allergic diseases, including allergic asthma, at Toronto Allergists in Toronto, ON, Canada, where he is also clinical director and managing partner. In addition, he is CEO of Evidence Based Medical Educator Inc in Toronto and the founder and chair of Urticaria Canada, an advocacy and patient support organization whose goal is to educate patients and health care professionals about chronic urticaria. Dr Lee earned a Doctor of Medicine degree from the Faculty of Medicine at the University of Toronto. He subsequently received fellowship training in internal medicine at the University of British Columbia in Vancouver, Canada, and in clinical immunology and allergy at the University of Toronto. Dr Lee's research interests include asthma, urticaria, nasal polyps, chronic cough, and atopic dermatitis. Among his accomplishments is working on the national consensus guidelines on immunoglobulin replacement therapy for secondary immune deficiencies and coauthorship of the original first paper on the use of dupilumab for chronic spontaneous urticaria in patients who had failed to respond to omalizumab. Dr Lee has served as section head of asthma at the Canadian Society of Allergy and Clinical Immunology and is currently a member of the Biologics and Therapeutics Committee of the American College of Allergy, Asthma, and Immunology.

ASTHMA MANAGEMENT: A REVIEW OF GINA RECOMMENDATIONS FROM 2019

Asthma is a chronic condition that affects more than 3.8 million people in Canada.[1] It is a condition that if not controlled may result in significant morbidity and mortality. Asthma is the leading cause of absenteeism from school and one of the leading causes of work loss through both absenteeism and presenteeism.[2] The direct costs of asthma, including hospitalization, healthcare professional services and medication and indirect costs, including decreased productivity, are estimated at $2.1 billion annually.[3] The cost of asthma to the Canadian economy is expected to climb to $4.2 billion annually by 2030.[4]

While many detrimental consequences of asthma stem from the condition itself, a significant proportion of the morbidity associated with asthma is also a result of systemic corticosteroids used to treat asthma exacerbations. There are many factors that lead to uncontrolled asthma, such as inappropriate and/or inadequate treatment of the condition. Access to appropriate treatment for realistic and achievable disease management, is critical in reducing the likelihood of experiencing an asthma exacerbation.

The Global Initiative for Asthma (GINA) Scientific Committee has developed a sophisticated set of procedures to review the world's literature with regard to asthma management and to update the GINA documents to reflect this state-of-the-art information.[5] The output is a report entitled *Global Strategy for Asthma Management and Prevention* complete with teaching slides and an abridged "pocket guide" of the main report's recommendations. All of this is made freely available at ginasthma.org. and includes an update to reflect the COVID-19 pandemic. The GINA report is not a set of guidelines but, rather, an "integrated evidence-based strategy focusing on translation into clinical practice"for health care practitioners with the goal of reducing both short- and long-term asthma exacerbations and adverse events.[6]

This article will focus on the key changes to the latest iteration of GINA recommendations for asthma management **(Figure 1)**.

NO MORE SHORT-ACTING BRONCHODILATORS ALONE

The largest fundamental change in asthma management occurred with the GINA 2019 recommendations. As of 2019, GINA no longer recommends treating adults or adolescents with asthma with short acting bronchodilators or short-acting ß Agonists (SABAs) alone. Instead, patients should receive intermittent symptom – driven (in mild asthma) or daily inhaled corticosteroids to reduce the risk of asthma exacerbations.

Many patients are referred with a diagnosis of 'mild' asthma, and a prescription for salbutamol PRN. It turns out there are significant downsides to this approach. Even mild asthmatics are at risk

of severe exacerbations and adverse events. For example, 30-37% of adults with acute asthma, 16% of patients with near fatal asthma, and 15-20% of adults dying of asthma had symptoms less-than-weekly in the previous three months.[7]

This may be a common misconception about asthma among health care professionals. It is in fact quite possible to have entirely normal lung function when someone is well, not having many symptoms of asthma and then suddenly deteriorate with severe symptoms, which may be triggered by a virus, allergen, or pollution exposure.

In the 1960s and 70s, asthma was essentially thought to be a disease of bronchospasm. As such, patients and some health care professionals felt that reliever medications, like SABAs, were sufficient for controlling asthma. Patients tended to receive rapid symptom relief with SABA treatment due to its quick onset of action. Although inhaled SABAs have been a first line treatment strategy for the management of asthma for more than fifty years, we may be required to update our disease management approach in 2021 in light of the evidence available to us.[8]

We now know that regular or frequent use of SABAs is associated with:

1. Beta receptor downregulation which causes decreased broncho-protection, rebound hyper-responsiveness, and ultimately decreased bronchodilator response[9]
2. Increased allergic responses, and increased eosinophilic airway inflammation[10]
3. Using more than or equal to three canisters of SABAs per year (average of 1.7 puffs/day) is associated with higher risk of emergency department visits[11]
4. Dispensing of twelve or more canisters per year is

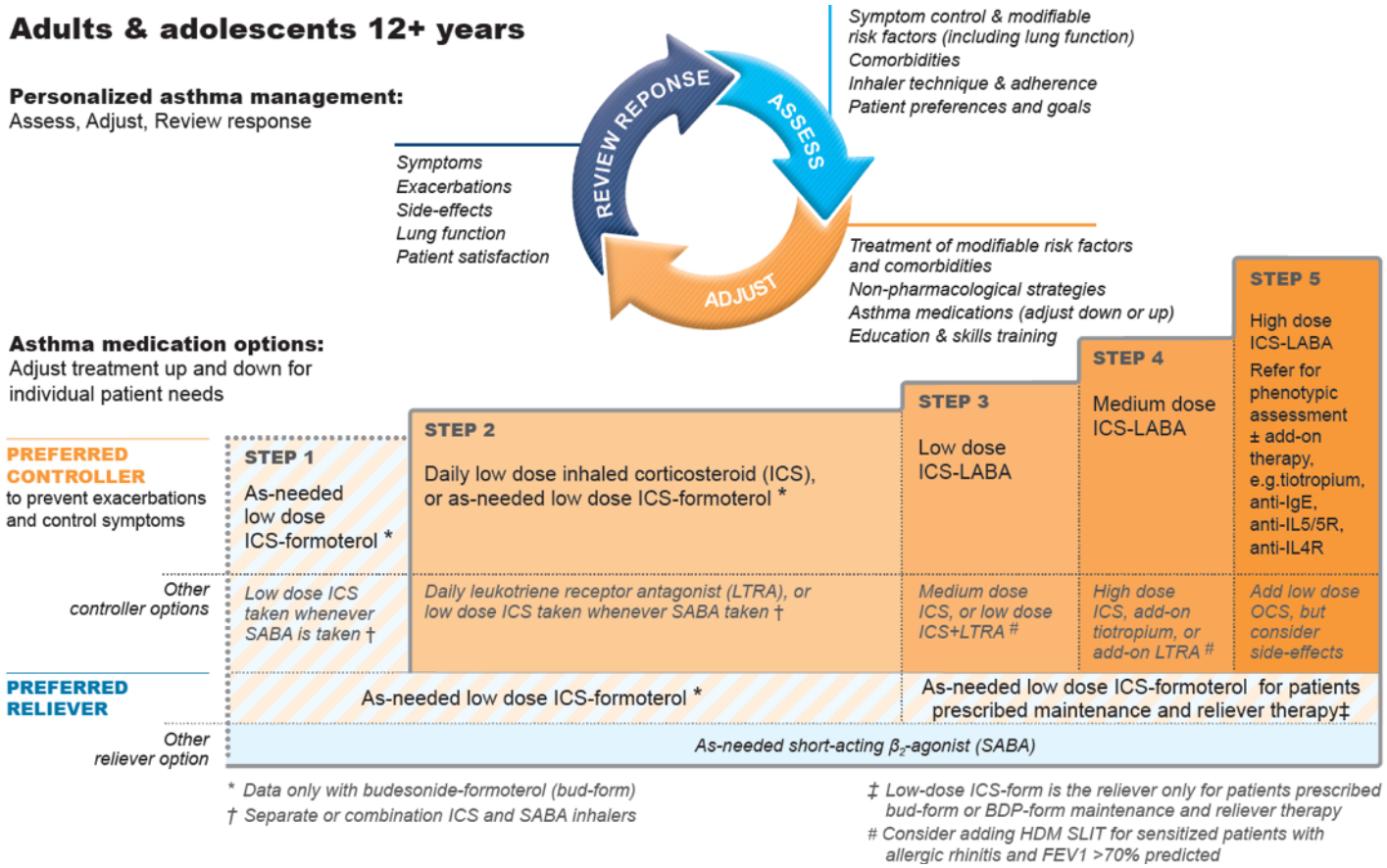

Figure 1. The 2019 Global Initiative for Asthma (GINA) treatment strategy figure for adults and adolescents, annotated to highlight key features.

ICS: inhaled corticosteroids; SABA: short-acting ß2-agonists; LTRA: leukotriene receptor antagonists; LABA: long-acting ß2-agonists; OCS: oral corticosteroids; BDP: beclometasone dipropionate; HDM: house dust mite; SLIT: sublingual immunotherapy; FEV1: forced expiratory volume in 1 s; IL: interleukin. Modified with permission of the Global Initiative for Asthma (www.ginasthma.org).

associated with higher risk of death[12]

Despite our knowledge of these issues, changes to disease management have not gained traction.

Looking at individual risk and extrapolating to a population level, one can imagine a tremendous benefit in risk reduction for asthma patients. This would be akin to the risk reduction observed when population-level algorithms model the impact of widespread use of statins and blood pressure medications to reduce the risk of coronary artery and cardiovascular disease.

INHALED STEROIDS (ICS) WITH FORMOTEROL [(A FAST-ACTING AND LONG-ACTING ß AGONIST (LABA)] IS THE BETTER APPROACH AT MANAGING MILD ASTHMA FOR ADULTS AND TEENS

Two breakthrough studies (SYGMA 1 and 2) both published in 2018 in the New England Journal of Medicine provide evidence for this approach of managing mild asthma for adults and teens. In SYGMA 1, a 52-week, double-blind trial involving patients 12 years of age or older with mild asthma, patients were randomly assigned to one of three regimens: terbutaline (0.5 mg) used as needed (terbutaline group), budesonide–formoterol (200 µg of budesonide and 6 µg of formoterol) used as needed (budesonide–formoterol group), or twice-daily budesonide (200 µg) plus terbutaline used as needed (budesonide maintenance group). The primary objective was to investigate the superiority of as-needed budesonide–formoterol to as-needed terbutaline with regard to electronically recorded weeks with well-controlled asthma.

A total of 4215 patients underwent randomization, and 4176 (2089 in the budesonide–formoterol group and 2087 in the budesonide maintenance group) were included in the full analysis set. Budesonide–formoterol used as needed was noninferior to budesonide maintenance therapy for severe exacerbations; the annualized rate of severe exacerbations was 0.11 (95% confidence interval [CI], 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16). The median daily metered dose of inhaled glucocorticoid was lower in the budesonide–formoterol group (66 µg) than in the budesonide maintenance group (267 µg). The time to the first exacerbation was similar in the two groups (hazard ratio, 0.96; 95% CI, 0.78 to 1.17). The change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy.[14]

Based on the conclusions of these studies and others, as needed inhaled corticosteroids (ICS) with fast-acting LABAs are nearly as good as using a regular ICS and as needed SABAs. However, the reality is that asthma patients are well known to have poor adherence to their medications for a variety of reasons, including but not limited to the fact that asthma symptoms routinely wax and wane as a hallmark of the condition, thereby lulling patients into a false sense of security around disease management and control. As such taking the ICS + LABA combination used as needed is a realistic approach which demonstrates good rates of reduction in asthma exacerbations and which is on par with taking daily ICS inhalers. Additionally, an ICS + LABA combination may also help to reduce the total dose of ICS.

SHARED DECISION MAKING AND PERSONALIZED ASTHMA MANAGEMENT IS KEY

Every patient and their response to their disease and medications is different. It is important to remember that a tailored approach to disease management is required. In particular, while teens and adults have a set of GINA recommendations, GINA has separate recommendations for children 6-11 years of age and for children 5 years of age and younger.

It is important that the physician have a good therapeutic rapport with patients where open and honest discussion about treatment goals are expressed. For example, patients may have steroid phobias or other misconceptions related to adverse effects of medications

that impair their ability to achieve optimal outcomes. If someone is forgetful or their lifestyle is not suited for daily therapy for mild asthma, they should be upfront about this so that modalities including the use of ICS + fast-acting LABAs can be discussed. Similarly, if a patient is more disciplined and can follow an asthma action plan or step-by-step instructions, this can be discussed in partnership with the physician in order to ensure optimal success of the treatment plan.

The goal of improved asthma outcomes is grounded in mutual trust and respect. Offering choice to patients is the correct approach. The goal is to make sure that there is mutual trust and respect so that in a real life situation, they can find a solution that is doable while still appropriate. Working toward lifestyle changes in particular such as weight loss, smoking cessation, or increasing physical activity can be better optimized with a trusted relationship.

SEVERE UNCONTROLLED ASTHMA

The definition of severe asthma for patients aged ≥ 6 years is asthma which requires treatment with guideline-suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/ theophylline) for the previous year or systemic CS for ≥ 50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.[15]

Uncontrolled asthma is defined as at least one of the following:

1) Poor symptom control: ACQ consistently ≥ 1.5, ACT < 20 (or not well controlled by NAEPP/ GINA guidelines)

2) Frequent severe exacerbations: two or more bursts of systemic CS (3 days each) in the previous year

3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

4) Airflow limitation: after appropriate bronchodilator withhold forced expiratory volume in one second (FEV1) <80% of personal best (or < the lower limit of normal (LLN), in the face of reduced FEV1/ forced vital capacity (FVC) defined as less than the LLN)

There is not a consistently reliable and predictable way to choose an optimal biologic therapy for severe asthma patients since all current approved therapies for severe asthma involve type 2 inflammation. Type 2 immune responses can be induced by parasitic helminths and are associated with atopic diseases, such as allergy and asthma. Airway type 2 immune responses are mainly mediated by eosinophils, mast cells, basophils, TH2 cells, group 2 innate lymphoid cells (ILC2s) and IgE-producing B cells. Type 2 immune responses are characteristic of allergic rhinitis in the upper airways and asthma in the lower airways.[16] Unchecked activation of this repair mechanism of inflammation has many long term deleterious effects at the tissue site.

Currently, blood tests referred to as biomarkers to determine the type of severe asthma, all overlap and fluctuate for the same patient depending on the point in time at which the test was taken. In fact, the same patient can express different levels of biomarkers from morning to night owing to diurnal variation of the immune system.

Patients with severe asthma have typically maximized inhaler therapies and some oral therapies, yet still remain uncontrolled, experience symptoms and frequent exacerbations. The early use of biologic therapy for these patients is both correct and necessary. It should be guided by the atopic comorbidities of each patient. Treating a host of related conditions such as rhinitis, atopic dermatitis, urticaria, chronic sinusitis, depression, and anxiety is paramount to the optimal management of asthma.

THE IMMUNE SYSTEM IS COMPLEX, BUT OUR KNOWLEDGE IS IMPROVING

In summary, we are learning more about the shared immune basis for many conditions that involve the lung and that may also involve other body systems. The discovery of the existence of a newly-identified white blood cell called innate lymphoid cells (ILCs) suggests that several types of these cells exist in the lungs, brain, skin, and virtually every organ system.

Vivier et al note that "the discovery and investigation of ILCs over the past decade have changed our perception of immune regulation and how the immune system contributes to the maintenance of tissue homeostasis. We now know that cytokine-producing ILCs contribute to multiple immune pathways by, for example, sustaining appropriate immune responses to commensals and pathogens at mucosal barriers, potentiating adaptive immunity, and regulating tissue inflammation. Critically, the biology of ILCs also extends beyond classical immunology to metabolic homeostasis, tissue remodeling, and dialog with the nervous system."[17] This incredible scientific advance in our understanding of the immune system has allowed us to study new pathways to develop new treatments to help patients.

References:

1. Public Health Agency of Canada. Report from the Canadian Chronic Disease Surveillance System: Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Canada, 2018.

2. 15 Ontario Ministry of Health and Long-Term Care (2000). Taking Action on Asthma: Report of the Chief Medical Officer of Health. http://www.health.gov.on.ca/en/common/ministry/publications/reports/asthma/asthma2.aspx

3. Cost Risk Analysis for Chronic Lung Disease in Canada, The Conference Board of Canada, Louis Theriault, Gregory Hermus, Danielle Goldfarb, Carole Stonebridge, Fares Bounajm, March 15 2012 http://www.conferenceboard.ca/elibrary/abstract.aspx?did=4585

4. Ibid.

5. https://ginasthma.org/about-us/; accessed January 4th, 2021

6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org ; accessed January 4th, 2021

7. Dusser, D1, et al. "Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations." Allergy 62.6 (2007): 591-604.

8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org ; accessed January 4th, 2021

9. Hancox, R. J., et al. "Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled ß-agonist treatment." Respiratory medicine 94.8 (2000): 767-771.

10. Aldridge, R. E., et al. "Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma." American Journal of Respiratory and Critical Care Medicine 161.5 (2000): 1459-1464.

11. Stanford, Richard H., et al. "Short-acting ß-agonist use and its ability to predict future asthma-related outcomes." Annals of Allergy, Asthma & Immunology 109.6 (2012): 403-407.

12. Suissa, Samy, et al. "A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists." American journal of respiratory and critical care medicine 149.3 (1994): 604-610.

13. O'Byrne, Paul M., et al. "Inhaled combined budesonide–formoterol as needed in mild asthma." New England Journal of Medicine 378.20 (2018): 1865-1876.

14. Bateman, Eric D., et al. "As-needed budesonide–formoterol versus maintenance budesonide in mild asthma." New England Journal of Medicine 378.20 (2018): 1877-1887.

15. Chung, Kian Fan, et al. "International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma." European respiratory journal 43.2 (2014): 343-373.

16. Fahy, John V. "Type 2 inflammation in asthma—present in most, absent in many." Nature Reviews Immunology 15.1 (2015): 57-65.

17. Vivier, Eric, et al. "Innate lymphoid cells: 10 years on." Cell 174.5 (2018): 1054-1066.