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Are the 2019 Global Initiative for Asthma (GINA) strategy recommendations applicable to the Canadian context?

A conversation between the Canadian Thoracic Society Asthma Assembly and Professor Helen Reddel, Chair of the GINA Scientific Committee

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In 2019, the GINA committee asserted what is arguably one of the most profound changes in the management of asthma in the last 30 years: **treatment of asthma with short acting beta agonists (SABA) alone, taken as needed, is no longer recommended for adults and adolescents.**

The present document aims to present the context of this change and discuss its potential applicability in the Canadian landscape in a question and answer format. A **systematic review of the evidence is currently being undertaken by a CTS Asthma Guideline Panel and new CTS recommendations will be presented after completing a formal review.**

The new GINA recommendations are summarized in the following boxes.

Adolescents (>12 years old) and adults:

1. *Treatment of asthma with SABA alone is not recommended*
2. *Patients with symptoms less than twice a month and no exacerbation risk factors (GINA Step 1): the preferred therapy is low-dose inhaled corticosteroid (ICS)-formoterol taken on a PRN basis for symptom relief. Other controller options include taking a low dose ICS inhaler whenever a SABA inhaler is taken (using separate or combination inhalers).*
3. *Patients with symptoms twice a month or more, or with risk factors for exacerbation (GINA Step 2): the recommended therapy is either daily low-dose ICS with as-needed SABA or low dose ICS-formoterol as needed. Other controller options include leukotriene receptor antagonists, or taking low dose ICS whenever a SABA inhaler is taken.*

Children 6 to 11 years old:

1. *Patients with symptoms less than twice a month and no exacerbation risk factors (GINA Step 1): the recommended therapy is as-needed SABA. Other options to provide controller treatment are taking low-dose ICS inhaler whenever a SABA is taken, or daily low dose ICS with as-needed SABA*
2. *Children with symptoms twice a month or more, or with risk factors for exacerbations (GINA Step 2): the recommended therapy is daily low dose ICS with as-needed SABA. Other controller options are leukotriene receptor antagonist, or taking low dose ICS inhaler whenever a SABA inhaler is taken.*

Dr. Helen Reddel

Professor Reddel is a respiratory physician and research leader at the Woolcock Institute of Medical Research, University of Sydney, Australia. She is Chair of the Science Committee for Global Initiative for Asthma (GINA), Clinical Adviser to the Australian Center for Airways disease Monitoring (ACAM), and international co-chair of the large observational NOVELTY study. Dr. Reddel's current research interests focus on characterizing the clinical trajectories and the underlying mechanisms of airways disease, practical strategies to improve asthma management, and qualitative research about the experience of living with mild or severe asthma. She has a strong focus on improving communication between patients and health professionals, and on making guidelines not only evidence-based, but also practical and practice-centered.

Questions and answers

The evidence base

Q1: Dr. Reddel, could you summarize the context and evidence base that led to these major changes in the GINA 2019 Global Strategy?

A: SABAs have been first-line treatment for asthma since the 1950s, when asthma was considered a disease of bronchoconstriction. Its inflammatory nature was confirmed in the 1970s, and the risks of SABA-only treatment and of SABA overuse were documented in the 1980s-2000s following epidemics of asthma deaths. Low dose ICS improved symptom control and reduced the risk of severe exacerbations, even in patients with mild asthma; and in moderate-severe asthma, risk was further reduced by ICS-formoterol maintenance and reliever therapy. However, clinical guidelines continued to recommend that patients with infrequent, mild or short-lived asthma symptoms should be treated with SABA alone, and furthermore, adherence with ICS was known to be poor. It therefore seemed logical to GINA to investigate as-needed low dose ICS-formoterol *alone* for mild asthma, to reduce the risk of severe exacerbations without the need for daily treatment. In 2007, GINA members began applying for funding for such studies, submitting multiple protocols over subsequent years to manufacturers of ICS-formoterol and other funding bodies, with approval finally obtained in 2014 for two large regulatory studies, SYGMA 1 and 2, that were published in 2018.^{1,2}

The evidence base for the GINA 2019 recommendations, published in April 2019, included extensive evidence about the risks of SABA-only treatment and SABA over-use, the SYGMA studies,^{1,2} studies of as-needed low dose budesonide-formoterol for exercise-induced bronchoconstriction³ and high dose budesonide-formoterol for acute severe asthma,^{4,5} and three studies of ICS taken whenever SABA was taken.⁶⁻⁸ Further publications since then include two open-label studies of as-needed budesonide-formoterol^{9,10} and an additional study of ICS whenever SABA is taken.¹¹

Q2: Recent publications, SYGMA 1 and 2, and Novel START, studied the use of budesonide-formoterol prn in mild asthma. However, it appears that GINA has recommended the use of budesonide-formoterol as a reliever across the entire spectrum of asthma severity. Can you clarify if this is what GINA has recommended, and discuss the rationale and evidence to support this?

A: We have become aware of a misunderstanding around this issue, and welcome the opportunity for clarification. Although GINA recommends as-needed ICS-formoterol as a preferred reliever across the whole spectrum of asthma severity, this does not apply to all patients in Steps 3-5. There, as stated in the GINA treatment figure and text since 2014, low dose ICS-formoterol is the reliever *only* for adult and adolescent patients prescribed maintenance and reliever therapy with low dose budesonide-formoterol or beclomethasone-formoterol. For patients prescribed other ICS-LABA combinations in Steps 3-5, their reliever is still SABA (as before), as there would be safety concerns about combining different LABAs. However, for such patients, clinicians should be alert to the potential for poor adherence, as this would leave the patient exposed to the risks of SABA-only treatment.

Q3: In the SYGMA trials, asthma control was better in patients on daily budesonide + PRN terbutaline versus those on PRN budesonide/formoterol. Given these results and the safety of daily low dose ICS, why didn't GINA recommend daily ICS as the preferred controller option in those with persistent asthma (Step 2) and have PRN budesonide/formoterol as an "other controller option" in those with poor adherence to daily medication?

A: In recommending as-needed low dose ICS-formoterol as one of the two preferred controller options for Step 2, GINA placed

high importance on the evidence from the two SYGMA studies (~8000 patients) that this strategy reduced the risk of severe exacerbations to a similar extent as maintenance ICS, without the need for daily treatment.^{1,2} A lower importance was placed on the small, non-cumulative differences in standard measures of asthma symptom control (e.g. Asthma Control Questionnaire (ACQ-5) difference of ~0.15 compared with the minimal clinically important difference of 0.5); and in pre-bronchodilator FEV₁ (difference ~30mL).^{1,2} The primary outcome measure in SYGMA 1 that had been agreed between the study Sponsor and the regulator, i.e. electronically-recorded well-controlled asthma weeks, was based on older concepts of asthma control,¹² had never been calculated from electronically recorded data, and is not feasible for use in clinical practice.

Q4: In the TREXA trial, which included children 6 to 18 years old, time to exacerbation was longer with daily beclomethasone + PRN SABA in comparison to beclomethasone + SABA PRN. In addition, there was no added benefit of ICS + SABA PRN compared to SABA PRN as a reliever in those on daily ICS. Given the limited number of children 12-18 included in adult trials, do you feel that the evidence base supports the new GINA recommendations in children 12-18?

A: During the GINA discussions about mild asthma, no specific concerns were raised about children aged 12- <18 years. With maintenance and reliever therapy, the reduction in severe exacerbations among 1847 adolescents had been the same as for adult participants.¹³ The SYGMA studies included 889 children aged 12- <18 years; data for this sub-population were presented at ATS 2019. The TREXA study⁷ was much smaller, with 288 children aged 5-18 years randomized to four treatment arms. The outcomes in TREXA with as-needed ICS + SABA cannot be assumed to be the same as with as-needed ICS-formoterol, because as-needed formoterol itself reduces the risk of severe exacerbations compared with as-needed SABA.¹⁴

Q5: We acknowledge that the GINA report is not a guideline but rather an "integrated evidence-based strategy focusing on translation into clinical practice." Recommendations are framed, not as answers to isolated guideline questions, but as part of an integrated strategy to target GINA's goals of preventing asthma deaths and exacerbations, improving symptom control, its current understanding of underlying disease processes, human behavior, and implementation in clinical practice. Do you think that the GINA mandate gives the GINA committee greater latitude than a guideline panel to extend therapeutic recommendations to areas where the evidence base is not as strong?

A: We do not consider that GINA has greater latitude than a guideline panel to make recommendations that are not well supported by evidence. Three points should be considered here. First, national guidelines bodies themselves may be limited in the recommendations that they can make, because of lack of access to medications such as combination ICS-formoterol and/or local restrictions on making off-label recommendations. Each country and jurisdiction should determine at a local level the options best suited to their resources, needs and context.

Second, the primary recommendation by GINA was that, for safety, SABA-only treatment of asthma in adolescents and adults was no longer recommended.¹⁵ Potential therapeutic strategies for avoiding SABA-only treatment were then considered, and those with the highest quality evidence, and the strongest values and preferences, were recommended for "Preferred controller." However, GINA was aware that some countries or jurisdictions did not have access to low-dose ICS-formoterol, so we listed alternative strategies for avoiding SABA-only treatment (e.g. as-needed ICS + SABA) for which there was *some* evidence, albeit less substantial and/or lower in quality. These options were labeled as "Other [i.e. non-preferred] controller options." The

categories “Preferred controller” and “Other controller options,” respectively, correspond to GRADE’s “recommended” and “suggested” therapies.¹⁶

Third, for Step 1 options, i.e. for patients with symptoms less than twice a month and no risk factors for exacerbations, GINA placed a lower value on the fact that all evidence was indirect (from studies in patients eligible for Step 2 studies), and placed a high value on the fact that patients with such infrequent symptoms could have serious exacerbations but would be unlikely to take regular ICS if prescribed. A high value was also placed on the priority to avoid conflicting messages about SABAs for patients and clinicians between Step 1 and Step 2.¹⁵

Implementation challenges

Q6: GINA cites poor adherence to daily low-dose ICS as a rationale for recommending ICS-formoterol as needed as an equivalent option to daily low dose ICS in mild asthma. One concern with the ICS-formoterol as needed recommendation is that it reinforces the patient belief that asthma medication is needed only when you have symptoms which may be contrary to the provider perspective that a patient with minimal symptoms but at high risk for exacerbations, or with poor pulmonary function should take daily medication. How would you address this practitioner concern?

A: This issue is currently a major problem for guidelines that start treatment with SABA alone. There, the initial conversation is about symptom relief, for which patients quickly find SABA to be very satisfactory. However, later on, the message has to be switched to tell patients that they need to take regular daily treatment even when they have no symptoms, and the rationale that is given is to reduce their use of (the familiar and effective) SABA and to reduce their risk of exacerbations. Instead, with as-needed ICS-formoterol in mild asthma, the message to patients from the start of treatment is that this therapy will both relieve their symptoms and reduce their risk of severe exacerbations.

Q7: In Canada, there is only one combination therapy that has been approved by Health Canada as a controller and reliever: *budesonide-formoterol*. The other available combination therapy containing a fast acting LABA is the combination of mometasone and formoterol which has not been approved for use as a reliever. Do you think the use of mometasone/formoterol could be an alternative to the use of budesonide/formoterol as a reliever?

A: The dosage of mometasone-formoterol in the Product Information is 2 inhalations on each occasion (total 10mcg formoterol), so the formoterol dose would escalate rapidly with as-needed use. This is presumably why mometasone-formoterol has not been studied for maintenance and reliever therapy, although I understand that it is prescribed by some Canadian physicians with 1 inhalation per as-needed dose. A case could be made in Canada for a pragmatic study of as-needed mometasone-formoterol in mild asthma, one inhalation at a time, in order to have a second option for mild asthma. However, the pathway to a regulatory indication would be challenging.

Q8: In patients who are already taking another type of combination therapy, for example, fluticasone/salmeterol as a daily controller medication with SABA as needed, does GINA recommend that patients:

- continue fluticasone/salmeterol as a daily controller medication with SABA as needed if they are achieving symptom and exacerbation control; or
- continue to use fluticasone/salmeterol as a daily controller medication but change to ICS-formoterol as needed; or
- switch to an ICS-formoterol combination as a controller and reliever?

A: This question relates to patients currently prescribed Step 3–5 treatment with maintenance ICS-LABA plus as-needed SABA. As described above in Q2, option (b) is definitely NOT recommended, as there would be concerns about the safety of using two different LABAs. Options (a) and (c) can be presented for shared decision-making with the patient, based on the patient’s clinical context (including exacerbations in the previous 12 months, which would favor (c)), risk factors including environmental exposures, comorbidities, ability to use the inhalers, cost, and patient preference.

Health policy and planning

Q9: The recommendation to use ICS-formoterol as a reliever without a daily controller medication is currently off label for all of the available medications in Canada. This will create prescription and reimbursement challenges. What is the GINA perspective on making a recommendation for medication to be used in a way that has not yet been approved by national health authorities such as Health Canada?

(NOTE: budesonide/formoterol received approval in Canada as an anti-inflammatory reliever therapy on September 25, 2019 after this question was proposed to Dr. Reddel.)

A: The GINA Science Committee and Board held extensive discussions before deciding to make recommendations for mild asthma, knowing that some would, at least initially, be off-label in countries that had a regulatory framework for pharmacotherapy. A similar situation had been encountered in 2018 with long-term macrolides for moderate-severe asthma. Then, GINA had decided that, if a new indication for an existing treatment was supported by good quality evidence, and if there were no new safety concerns, we would be prepared to make an off-label recommendation. For mild asthma, the driving factor was that GINA was no longer prepared to actively recommend a treatment (SABA-alone) that was associated globally with significant risk of mortality and morbidity, now that evidence was available for efficacious alternatives. Further considerations were that regulators looked to guidelines bodies for a clinical perspective on new treatment options (so each may be waiting for the other), and that a GINA recommendation might encourage manufacturers to make a regulatory submission.

Q10: Given that there is only one ICS-formoterol drug approved for use in Canada as a reliever, this may create an impression of commercial bias. Can you address this concern for Canadian providers?

A: As above in Q7, this situation already exists in Canada for maintenance and reliever therapy. For mild asthma, resources that may be useful to counter this perception include an editorial published in *Eur Respir J*¹⁵ describing the multiple agencies that were approached, and the length of time that it took, before GINA members were successful in having the clinical trials funded; and the detailed description on the GINA website of how issues of potential conflict of interest are handled (available from <https://ginasthma.org/about-us/methodology/>).

Q11: Budesonide-formoterol as needed is almost 4 times the price of a SABA. Is there data to suggest that the switch to as-needed low-dose ICS-formoterol as the preferred reliever is cost-effective?

A: In each country, the cost to the health system and to patients (including the direct and indirect cost of exacerbations) will be important factors for consideration, depending on the price points agreed by payers. Cost-effectiveness analyses were incorporated into three of the four RCTs of as-needed budesonide-formoterol, and some of these results will be available soon.

Safety

Q12: Are there concerns for potential risks or side effects, such as linear growth impairment or adrenal suppression with the use of an ICS each time a reliever is given, particularly for patients who are already on a daily high dose of ICS?

A: With maintenance and reliever therapy, risk of corticosteroid side-effects appears lower than with conventional maintenance therapy plus as-needed SABA, because the risk of exacerbations requiring OCS is the same or lower, and this outcome is achieved at the same or lower dose of ICS.¹⁷ In the one maintenance and reliever study that included children, this regimen was associated with less adrenal suppression and greater linear growth compared with maintenance low dose ICS.¹⁸ In the TREXA study, linear growth was greater in children 5–18 years randomized to as-needed ICS + SABA or to SABA alone than to either of the maintenance low dose ICS regimens.⁷ In the SYGMA 1 and SYGMA 2 studies in mild asthma, the median daily ICS dose with as-needed budesonide-formoterol was 57 mcg and 66 mcg/day, respectively,^{1,2} suggesting that the risk of adverse effects of corticosteroids would be extremely low.

Where you can find more information?

The GINA report and updated PowerPoint slide deck can be downloaded from <https://ginasthma.org/reports/>

An editorial in European Respiratory Journal, explains the history and rationale for the key 2019 changes in mild asthma. This article is available on open access as follows:

Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management. *Eur Respir J* 2019; 53: 1901046 [<https://doi.org/10.1183/13993003.01046-2019>].

New CTS recommendations will be posted on <https://cts-sct.ca/> as soon as they are available.

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References

- O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med*. 2018;378:1865–1876. doi:10.1056/NEJMoa1715274.
- Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(20):1877–1887. doi:10.1056/NEJMoa1715275.
- Lazarinis N, Jørgensen L, Ekström T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax*. 2014; 69(2):130–136. doi:10.1136/thoraxjnl-2013-203557.
- Balanag VM, Yunus F, Yang PC, et al. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther*. 2006;19(2): 139–147. doi:10.1016/j.pupt.2005.04.009.
- Bateman ED, Fairall L, Lombardi DM, et al. Budesonide/formoterol and formoterol provide similar rapid relief in patients with acute asthma showing refractoriness to salbutamol. *Respir Res*. 2006;7(1):13. doi:10.1186/1465-9921-7-13.
- Papi A, Canonica GW, Maestrelli P, et al. Best Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med*. 2007;356(20):2040–2052. doi:10.1056/NEJMoa063861.
- Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9766):650–657. doi:10.1016/S0140-6736(10)62145-9.
- Calhoun WJ, Ameredes BT, King TS, Icitovic N, et al. Asthma Clinical Research Network of the National Heart LaBI. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA*. 2012;308(10):987–997.
- Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med*. 2019;380(21):2020–2030. doi:10.1056/NEJMoa1901963.
- Hardy *J, Baggott *C, Fingleton J, et al. on behalf of the PRACTICAL study team. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet*. 2019;394(10202):919–928. doi:10.1016/S0140-6736(19)31948-8.
- Sumino K, Bacharier LB, Taylor J, Chadwick-Mansker K, et al. A pragmatic trial of symptom-based inhaled corticosteroid use in African-American children with mild asthma. *J Allergy Clin Immunol Pract*. 2019. S2213–2198(19)30602-6.
- Bateman ED, Boushey HA, Bousquet J, et al. Goal Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170(8):836–844. doi:10.1164/rccm.200401-033OC.
- Jorup C, Lythgoe D, Bisgaard H. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. *Eur Respir J*. 2018;51:1701688. doi:10.1183/13993003.01688-2017.
- Pauwels RA, Sears MR, Campbell M, et al. Relief Study investigators. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J*. 2003;22(5):787–794. doi:10.1183/09031936.03.00055803.
- Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J*. 2019;53(6): 1901046. doi:10.1183/13993003.01046-2019.
- Schunemann HJ, Jaeschke R, Cook DJ, Committee ATSDdA, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med*. 2006;174:605–614. doi: 10.1164/rccm.200602-197ST.
- Patel M, Pilcher J, Pritchard A, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med*. 2013;1(1):32–42. doi: 10.1016/S2213-2600(13)70007-9.
- Bisgaard H, Le Roux P, Bjamer D, et al. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest*. 2006;130(6):1733–1743. doi:10.1378/chest.130.6.1733.