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Complete List of Authors:	Reddel, Helen; Woolcock Institute of Medical Research Fitzgerald, Mark; The University of British Columbia Bateman, Eric; University of Cape Town Bacharier, LB; Washington University in Saint Louis Becker, Allan; University of Manitoba Children's Hospital Research Institute of Manitoba Brusselle, Guy; University Hospital Ghent Buhl, Roland; University Hospital Mainz Department of Hematology Oncology and Pulmonology Cruz, Alvaro; Federal University of Bahia Fleming, Louise ; Imperial College London, Respiratory Paediatrics; Royal Brompton and Harefield NHS Foundation Trust, Respiratory Paediatrics Inoue, Hiromasa; Kagoshima University Graduate School of Medical and Dental Sciences Department of Dentistry Ko, Fanny; Chinese University of Hong Kong Faculty of Medicine Krishnan, J; University of Illinois Hospital and Health Sciences System Levy, Mark; Sessional GP and Clinical Lead, National Review of Asthma Deaths 2011-2014 Lin, Jiangtao; China-Japan Friendship Hospital Pedersen, Soren; Kolding Hospital Sheikh, Aziz; The University of Edinburgh Usher Institute of Population Health Sciences and Informatics Yorgancioglu, Arzu; Celal Bayar University School of Medicine Boulet, Louis-Philippe; Quebec Heart and Lung Institute; Laval University
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GINA 2019 – A FUNDAMENTAL CHANGE IN ASTHMA MANAGEMENT

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K Reddel[1], J Mark FitzGerald[2], Eric D Bateman[3], Leonard Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry Krishnan[12], Mark L Levy[13], Jiangtao Lin[14], Søren E Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17], Louis-Philippe Boulet[18]

1. Woolcock Institute of Medical Research, University of Sydney, NSW, Australia, and Chair of the GINA Science Committee
2. Respiratory Division, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
3. Division of Pulmonology & Department of Medicine, University of Cape Town and University of Cape Town Lung Institute, Cape Town, South Africa
4. Washington University and St. Louis Children's Hospital, St Louis, MO, USA
5. Section of Allergy and Clinical Immunology, Children's Hospital Research Institute of Manitoba, University of Manitoba, Canada
6. Ghent University Hospital, Ghent, Belgium
7. Pulmonary Department, Mainz University Hospital, Mainz, Germany
8. ProAR Foundation and Federal University of Bahia, Brazil
9. Department of Respiratory Paediatrics, Royal Brompton Hospital, London, United Kingdom
10. Department of Pulmonary Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan
11. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong
12. Breathe Chicago Center, University of Illinois at Chicago, Chicago, IL, USA
13. Sessional GP and Clinical Lead National Review of Asthma Deaths, United Kingdom, and Chair of the GINA Dissemination and Implementation Committee

14. China-Japan Friendship Hospital, Peking University, Beijing, China

15. Kolding Hospital, Kolding, Denmark

16. Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, United Kingdom

17. Celal Bayar University, Medical Faculty, Department of Pulmonology, Manisa, Turkey

18. Québec Heart and Lung Institute, Laval University, Québec City, Canada, and Chair of the GINA Board

Corresponding author:

Professor Helen Reddel, Woolcock Institute of Medical Research, The University of Sydney, NSW, Australia

Phone: +61 2 9114 0437

Fax: +61 2 9114 0011

Email: helen.reddel@sydney.edu.au

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In April 2019, the Global Initiative for Asthma (GINA, see Box) published new recommendations that might be considered the most fundamental change in asthma management in 30 years. The new recommendations follow a decade-long programme of work by GINA, prompted by concerns about the risks and consequences of the long-standing approach of commencing asthma treatment with short-acting beta$_2$-agonists (SABA) alone. These initiatives were aimed at obtaining evidence about effective treatment options for mild asthma and providing consistent messaging for patients and clinicians across the spectrum of asthma severity. ***For safety, GINA no longer recommends treatment of asthma in adolescents and adults with SABA alone. Instead, to reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing treatment.*** Here, we provide the background to these recommendations, summarise the evidence and rationale for the changes, and identify research gaps.

The risks of SABA were the focus of extensive research in the 1980s and 1990s following two international epidemics of asthma deaths,[1] with case-control studies showing that over-use of SABA was associated with increased risk of asthma-related death.[2, 3] Randomised controlled trials (RCTs) found no advantage in regular versus as-needed SABA,[4, 5] and by the late 1990s, most guidelines recommended as-needed rather than regular SABA. In parallel, extensive evidence emerged of the protective value of regular ICS, with a dramatic reduction in the risk of asthma-related hospitalisations and death.[6, 7] Large RCTs demonstrated that in mild asthma, low dose ICS reduced severe exacerbations by ~50%, as well as controlling symptoms and improving quality of life.[8, 9] However, acceptance of daily ICS was slow, partly based on physician concern about the serious side-effects seen with oral corticosteroids.[1] Concern about b2-agonist risks in asthma largely shifted to long-acting b$_2$-agonists (LABA), with recommendations against LABA-only treatment, but in guidelines, SABA-only treatment remained unchallenged as the initial therapy for mild asthma, with ICS use recommended only for patients with frequent symptoms.

In 2007, GINA began actively searching for and reviewing evidence about treatment options for mild asthma, with a focus on reducing the risk of asthma-related exacerbations and death compared with SABA-only treatment. Multiple studies had demonstrated adverse effects of even

short-term regular use of SABA-alone, including reduced bronchoprotection and bronchodilator response, increased airway hyperresponsiveness, exercise-induced bronchoconstriction and allergic responses, and increased eosinophilic inflammation and mast cell mediator release.[10, 11] In health administrative database studies, patients with a lower ratio of ICS to SABA were at greater risk of hospitalisation and urgent admission,[12] whereas population-based strategies that increased access to ICS were associated with reduced hospitalisations and deaths.[13, 14] However, adherence with ICS is poor in real life, often only 25-35% of the prescribed dose,[15] leaving patients exposed to the risks of SABA-only treatment.[16] Multiple factors contribute to poor adherence,[17] including lack of perceived necessity (especially if symptoms are few[18]), perceived and actual side-effects, and cost; and few interventions have been effective in improving adherence.

Of particular concern to GINA was the paradoxical switch in messaging for patients and clinicians between Step 1, where symptom relief was the priority and SABA use was encouraged, and Step 2, where patients were told that they should reduce what was to them, a familiar, effective, low-cost treatment, and that to achieve this, they should take a daily treatment even when asymptomatic.[19, 20] Patient reliance on SABA was further reinforced by its prominent use in the trusted environments of emergency department and hospital care.

From 2007, based on evidence that exacerbations were significantly reduced by low dose ICS-formoterol maintenance and reliever therapy in moderate-severe asthma[21] and, in a study by Papi *et al*,[22] by as-needed beclometasone dipropionate (BDP)-salbutamol in patients stepping down from moderate dose ICS, GINA members repeatedly submitted proposals for studies of as-needed controller in mild asthma. For this purpose, the combination of ICS-formoterol was preferred over ICS-SABA as it was more widely available, and because of adverse outcomes with regular use of ICS-SABA in the study by Papi *et al*.[22] The aim of the GINA proposals was to improve management of mild asthma by a strategy that would reduce the risk of severe exacerbations while also being concordant with patient behaviour, beliefs and preferences.

The need for such studies was supported by the findings of the UK National Review of Asthma Deaths in 2014 that 9% of asthma deaths were in patients being treated with SABA-alone (suggesting that their physician had considered they had mild asthma), and 39% were associated with excess prescriptions for SABA.[23] In 2014, GINA recommended that SABA-only treatment should be restricted to patients with symptoms twice a month or less and with no risk factors for exacerbations. However, it was recognised that this cutpoint was arbitrary, and that patients with infrequent symptoms would be unlikely to be adherent with daily ICS, reverting to SABA-only treatment. In addition, there was a paucity of evidence for feasible alternatives. The first studies that were able to fill this gap were the large SYGMA studies of as-needed budesonide-formoterol in mild asthma, published in 2018.[24, 25]

In 2019, GINA undertook a comprehensive review of evidence on the adverse outcomes of SABA-only treatment and the impact on asthma exacerbations and deaths of any form of ICS in mild asthma, and resolved that there was now sufficient evidence to recommend that adults and adolescents with asthma should not be treated with SABA alone. Instead, they should receive either symptom-driven (in mild asthma) or daily ICS-containing treatment, to reduce their risk of serious exacerbations. Several treatment options for achieving this are recommended in the GINA 2019 strategy report (Figure).

For *Step 2* (for patients with symptoms twice a month or more, **or** with risk factors for exacerbations), the previous recommendation for *daily low dose ICS* remains. In making this recommendation, high importance was given to the weight of evidence that ICS reduces asthma-related deaths,[6] and that it reduces exacerbations even in so-called 'intermittent' asthma.[26] However, before choosing this option, the clinician should consider whether a patient is likely to be adherent with daily ICS, or default to SABA-only treatment with its attendant risks. The other 'preferred controller option' for Step 2 is *as-needed low dose ICS-formoterol.* Here, high importance was given to the almost two-thirds reduction in severe exacerbations seen with this treatment when compared with SABA alone,[25] and non-inferiority to daily ICS for severe exacerbations in SYGMA 1 and 2, achieved without the need for daily treatment and at a considerably lower dose of ICS (a quarter or less).[24, 25] Lower importance was given to small

non-cumulative differences seen in the SYGMA studies[24, 25] for FEV_1, (~30-50mL), symptom control (difference in Asthma Control Questionnaire (ACQ-5) ~0.15 vs MCID 0.5), and symptom-free days (mean difference 10.6 days per year) compared with regular ICS. When ICS-formoterol was used as-needed and pre-exercise, protection against exercise-induced bronchoconstriction was obtained, of similar magnitude to that obtained with regular ICS plus as-needed and pre-exercise SABA.[27] Evidence to date for as-needed ICS-formoterol is based on studies with low dose combination budesonide-formoterol, but low dose BDP-formoterol could potentially be used in the same way, given its effectiveness in maintenance and reliever therapy.[28]

GINA also provides additional as-needed controller options for Step 2 strategies that may reduce exacerbations, albeit with limited evidence. The option of *taking ICS whenever SABA is taken* is based on one study with as-needed combination BDP-salbutamol,[22] and two studies (one in 5-18 year-olds[29] and one in adults[30]) with separate ICS and salbutamol inhalers, in which exacerbations were reduced compared with SABA-alone and reduced or the same compared with regular ICS, at an average of ~15-25% of the ICS dose. Leukotriene receptor antagonists are still included as a Step 2 option, but they are non-preferred as they are less effective than daily ICS for preventing exacerbations and do not avoid the need for a reliever.[31]

Step 1 is for patients with symptoms less than twice a month. Here, no direct evidence is available, but the rationale for the 'preferred' controller option of as-needed ICS-formoterol, or for taking ICS whenever SABA is taken, is based on indirect evidence from the corresponding Step 2 studies. In formulating the Step 1 recommendations, high importance was given to prevention of severe exacerbations, and to avoidance of contradictions in asthma messaging between Step 1 and Step 2. Regular ICS is not recommended for Step 1, because it was considered extremely unlikely that patients with such infrequent symptoms would be prepared to take a daily treatment.

Currently, all of these as-needed strategies are technically 'off-label', as ICS, ICS-formoterol and ICS-SABA are indicated only for regular use in most countries. However, the safety of ICS-formoterol has been established over many years, including with maintenance and reliever

therapy,[32] and no new safety signals emerged in the recent large studies.[24, 25] Combination ICS-SABAs are available in a few countries, but with limited safety data.

The changes recommended in GINA 2019 represent a major reorientation in how we treat the largest group of asthma patients. In recommending these changes, GINA recognises that there are questions to be addressed, including the cost of implementation in low and high income countries; pharmacoeconomic analyses are underway. Exacerbations are infrequent events in mild asthma; in the closely-monitored SYGMA 1 study, only 12% of patients receiving as-needed SABA experienced a severe exacerbation in 12 months.[25] However, unusually among chronic diseases, patients with apparently mild asthma are over-represented in serious outcomes: 30–37% of adults with acute asthma, 16% of patients with near-fatal asthma, and 15–20% of adults dying of asthma had asthma symptoms less than weekly in the previous three months.[33] Controller treatment for mild asthma represents a population-level risk reduction strategy, similar to treatment of hypertension or hypercholesterolaemia, where one cannot know whether any individual patient has avoided a serious outcome. Large long-term studies would be needed to identify patients for whom it would be safe (in terms of risk of severe exacerbations or death) to treat without any ICS. There is no contradiction in employing a background population-level risk reduction strategy as part of personalised asthma management, as shown in the Figure.

Additional studies, already underway, will provide further evidence about the utility and implementation of these strategies in clinical practice. These include two open-label RCTs, representing the way that patients would use as-needed ICS-formoterol in real life;[34, 35] both of these studies include Type 2 biomarkers at baseline and during treatment. Qualitative research has been conducted to provide the patient perspective on treatment regimens in mild asthma.

Studies of as-needed ICS-formoterol are still needed in children, where reliance on SABA is currently established and maintained. There is only one study to date of as-needed ICS+SABA in children,[29] and none with as-needed ICS-formoterol. Other populations in whom as-needed ICS-formoterol should be investigated include pregnant women, where protection from exacerbations with a very low dose of ICS may be particularly attractive; and patients with seasonal allergic

asthma. Studies of airway hyperresponsiveness, and of the relationship between symptoms, lung function and use of ICS-formoterol reliever are needed, in order to understand the mechanism by which exacerbations are reduced. Head-to-head studies of as-needed ICS-formoterol and ICS-SABA are needed, to compare efficacy and safety.

As a global initiative, GINA aims to improve asthma care by presenting evidence-based treatment options. Explicitly, it recognises that each country and jurisdiction must work out at local level the options best suited to their resources and needs. Although the public health implications of these major changes in GINA recommendations remain to be studied, their potential is great both in economically developed and in low-income countries where access to ICS-containing medications, particularly as maintenance therapy, is limited or non-existent. Although budesonide-formoterol is now included in the World Health Organization list of Essential Medicines, it is not currently available or affordable in many countries, but changes in treatment policies provide the opportunity for motivating for greater access to this simplified form of care. These are also the countries in which the burden of potentially preventable asthma hospitalisations and deaths are greatest and in which the cost-effectiveness of the new approach might be best seen. Regular ICS maintenance treatment has been around for more than 40 years. Even in resource-rich countries, despite the best efforts of health professionals, adherence to maintenance treatment with ICS in mild asthma remains a distant hope. 2019 may represent the start of a new chapter for patients with mild asthma.

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The authors are members of the GINA Science Committee and/or the GINA Board.

Box – What is GINA?

The Global Initiative for Asthma (GINA) was established by the World Health Organization and the National Heart Lung and Blood Institute in 1993 to increase awareness about asthma among health professionals, public health authorities and the community, and to improve asthma prevention and management through a coordinated worldwide effort. GINA prepares scientific reports on asthma, encourages dissemination and implementation of the recommendations, and promotes international collaboration on asthma research. GINA does not accept donations. The work of GINA is supported only by the sale and licensing of GINA reports and its other publications, and by the voluntary work of GINA committee members.

The GINA report, which is updated annually, comprises an integrated strategy focusing not only on evidence, but also on translation into clinical practice. Evidence is considered and recommendations are framed, not as discrete questions, but in the context of their relationship to the overall goals of treatment, underlying disease processes, feasibility for implementation in clinical practice, evidence about human behaviour (of health professionals and of patients/carers), and variation in populations, health systems and medication access in different countries. The GINA strategy has a strong focus on preventing asthma-related deaths and severe exacerbations, as well as on efficacy and effectiveness for symptom control and lung function, and it promotes personalised treatment decisions across the spectrum of asthma severity.

The GINA 2019 report and other GINA publications, together with a description of GINA methodology, can be purchased, or downloaded free for personal use, from the GINA website, www.ginasthma.org.

Figure title:

The 2019 GINA treatment strategy figure for adults and adolescents, annotated to highlight key features

Footnote: Modified with permission of the Global Initiative for Asthma

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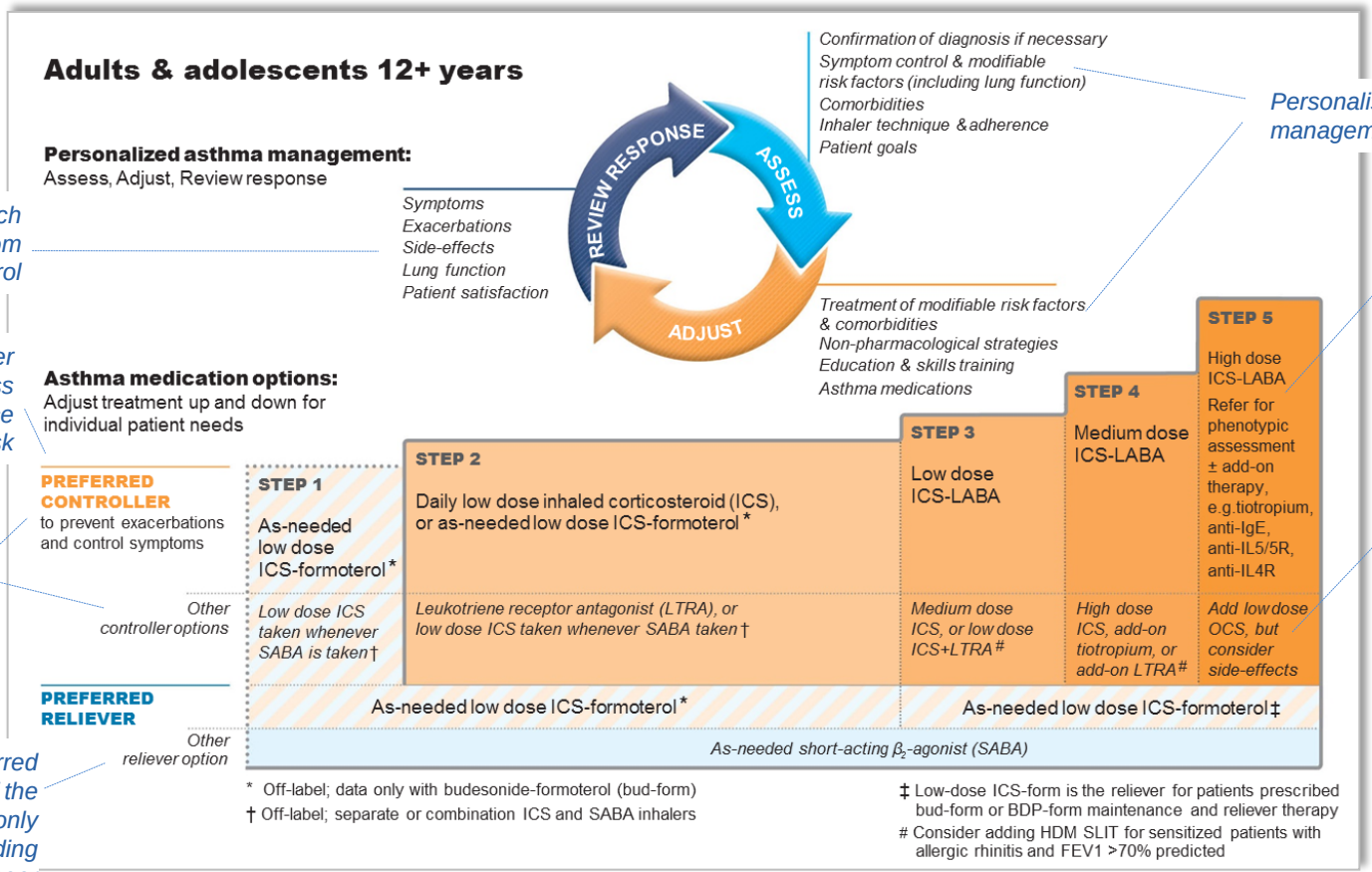
Figure: The 2019 GINA treatment strategy figure for adults and adolescents, annotated to highlight key features



A holistic approach – not just symptom control

ICS-containing controller is recommended across all severities to reduce exacerbation risk

'Preferred' and 'other' options are provided at each step, based on evidence

SABA is not a preferred reliever because of the risks of SABA-only treatment, including if adherence is poor

Personalised asthma management

See 2019 GINA Severe Asthma Pocket Guide for more details about Steps 4-5

Maintenance OCS is not a preferred option at Step 5 because of serious side-effects