



A Proposed Revision of the Stepwise Treatment Algorithm in Asthma

To the Editor:

The stepwise approach to the pharmacologic treatment of asthma is a core foundation of asthma guidelines (1). Through this approach, treatment intensity is increased in discrete steps to obtain symptom control and reduce exacerbation risk and is decreased after a period of prolonged control. The stepwise approach is usually shown by an algorithm, as illustrated in the 2020 Global Initiative for Asthma (GINA) strategy update (Figure 1). Here, we review the 2020 GINA stepwise algorithm and suggest alternative evidence-based algorithms that address potential problems with the currently recommended approach.

Currently at each step, the GINA algorithm aligns treatment recommendations based on inhaled corticosteroid (ICS)/formoterol reliever therapy with those of the traditional short-acting β_2 -agonist (SABA) reliever therapy. This assumes that the efficacy of treatment incorporating ICS/formoterol reliever therapy at each step aligns more closely with the corresponding alternative treatment incorporating a SABA reliever at the same step, rather than at adjacent higher or lower steps, which is not the case (2–4). This is illustrated by the recent systematic review and network meta-analysis that reported that the relative risk of a severe exacerbation with low-dose ICS/formoterol maintenance and reliever therapy at GINA step 3 compared with low-dose ICS/long-acting β_2 -agonist (LABA) plus SABA therapy (GINA step 3), medium-dose ICS/LABA plus SABA (GINA step 4), and high-dose ICS/LABA plus SABA (GINA step 5) was 0.55 (95% confidence interval [CI], 0.47–0.64), 0.71 (95% CI, 0.56–0.91), and 0.78 (95% CI, 0.51–1.21) respectively (3). Thus, low-dose ICS/formoterol maintenance and reliever therapy at GINA step 3 aligns most closely in terms of efficacy with high-dose ICS/LABA plus SABA therapy at GINA step 5 and then progressively aligns to a lesser extent with medium-dose ICS/LABA plus SABA therapy at GINA step 4 and then with low-dose ICS/LABA plus SABA therapy at GINA step 3. This ranking of efficacy is thus discordant with the current algorithm. This structural problem could be resolved by separating the instructions for the stepwise approach incorporating ICS/formoterol reliever therapy from those incorporating SABA reliever therapy by using two separate algorithms, as was undertaken in the New Zealand asthma guidelines in 2020 (5). This avoids the problem of step misalignment and the potential inadvertent mixing of the two approaches. It is possible to simplify the

algorithms further by not including other less effective “second-line” alternative treatments.

The antiinflammatory reliever-based algorithm using ICS/formoterol can be based on four steps, the first step being use of ICS/formoterol as the sole reliever therapy (Figure 2A), which is currently proposed at GINA steps 1 and 2 (Figure 1). Steps 2 and 3/4 are use of “standard”-dose (low-dose) and “higher”-dose (medium-dose) ICS/formoterol maintenance and reliever therapy, corresponding to the current GINA steps 3 and 4/5; the add-on therapies in severe asthma are introduced at step 4 (currently GINA step 5) (Figures 1 and 2A). The antiinflammatory reliever-based algorithm can be considered the preferred strategy, as it outperforms the traditional SABA reliever-based algorithm at each step in reducing the risk of severe exacerbations (2–4).

The traditional SABA reliever-based algorithm can also comprise four steps (Figure 2B). With the recommendation that a SABA should no longer be used as the sole reliever therapy without an ICS (1), regularly scheduled maintenance ICS therapy together with SABA reliever therapy (currently one of the preferred treatment options at GINA step 2) is recommended for step 1. At steps 2 and 3/4, “standard”-dose (low-dose) and “higher”-dose (medium- or high-dose) maintenance ICS/LABA and SABA reliever therapies are recommended, corresponding to the current GINA steps 3 and 4/5; the add-on therapies in severe asthma are introduced at step 4 (previously GINA step 5). Although the option to prescribe either medium- or high-dose ICS/LABA therapy is provided, including them at the same step is based on the similar efficacy yet greater risk of adverse systemic effects with the high-dose ICS regimen (6) and the known reluctance to step down from high doses of ICS/LABA therapy (7), which may contribute to the common prescription of inappropriately excessive doses of ICSs (6).

One of the main uncertainties with both algorithms is the paucity of evidence on which to base the thresholds for changing treatment steps, a limitation that is shared with the current GINA algorithm (8). Current evidence suggests that the presence of biomarkers of type 2 airway inflammation is the most effective way to identify patients likely to respond to higher-intensity ICS treatment (9). In their absence, a reasonable approach is to base changes in treatment on two key factors, namely whether there has been a recent severe exacerbation and the frequency of reliever use. A severe exacerbation could prompt medical review for consideration of an increase in the treatment step, as such an event is associated with an increased risk of future severe exacerbations (10). Transition points based on high SABA use could be used for the traditional SABA reliever-based algorithm, as increasing use is a marker of poor asthma control and exacerbation risk (10, 11). However, there is a different relationship with increasing ICS/formoterol use, in which higher use reduces the level of risk of an exacerbation, compared with SABA use (11). This could be addressed by guiding the patient to assign the higher reliever use to a higher regularly scheduled maintenance dose for the period of increased use. For both algorithms, “treatable traits” would be identified and managed in their own right (9).

In conclusion, the scientific evidence that ICS/formoterol reliever therapy is more effective at reducing severe exacerbation risk than SABA reliever therapy, either alone or when received together with maintenance ICS/formoterol therapy, has led to a paradigm shift in asthma management, which has the potential to cause confusion, as it replaces the long-established clinical practice that all patients should receive SABA reliever therapy. The potential confusion is evident from the current stepwise treatment algorithm’s complexity, due to the

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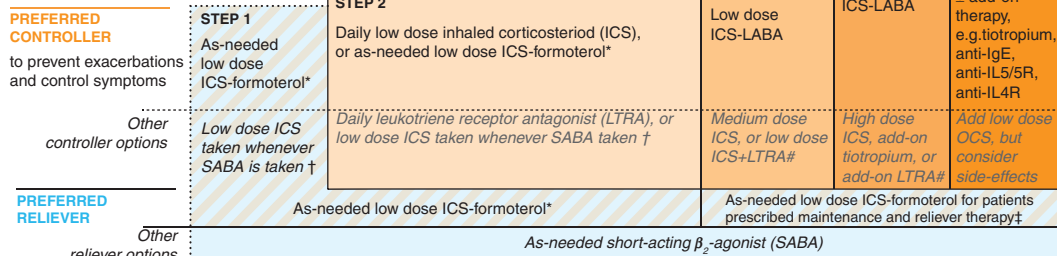
Adults & adolescents 12+ years

Personalized asthma management:

Assess, Adjust, Review response

Asthma medication options:

Adjust treatment up and down for individual patient needs



* Data only with budesonide-formoterol (bud-form)

† Separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 > 70% predicted

Figure 1. Personalized management for adults and adolescents to control symptoms and minimize future risk. The 2020 Global Initiative for Asthma algorithm. Reprinted by permission from Reference 1. BDP = beclomethasone dipropionate; HDM = house dust mite; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroids; SABA = short-acting β_2 -agonist; SLIT = sublingual immunotherapy.

attempt to represent all treatment options, and the inclusion of two reliever therapy regimens with differing efficacy in a single figure (Figure 1). These structural problems can be addressed by separating the current algorithm into two separate algorithms based on anti-inflammatory ICS/formoterol and SABA reliever therapy strategies. The priority now is to investigate the practical implementation of the algorithms to better inform their use in clinical practice. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Richard Beasley, D.Sc.*
Medical Research Institute of New Zealand
Wellington New Zealand

Victoria University of Wellington
Wellington, New Zealand
and

Capital & Coast District Health Board
Wellington, New Zealand

Pepa Bruce, M.B. B.S.
Medical Research Institute of New Zealand
Wellington New Zealand

Lee Hatter, M.B. B.S.
Medical Research Institute of New Zealand
Wellington New Zealand

and
Imperial College London
London, United Kingdom

Irene Braithwaite, Ph.D.
Alex Semprini, Ph.D.
Ciléin Kearns, M.B. Ch.B.
Medical Research Institute of New Zealand
Wellington New Zealand

Mark Weatherall, M.Appl.Stats.
Capital & Coast District Health Board
Wellington, New Zealand

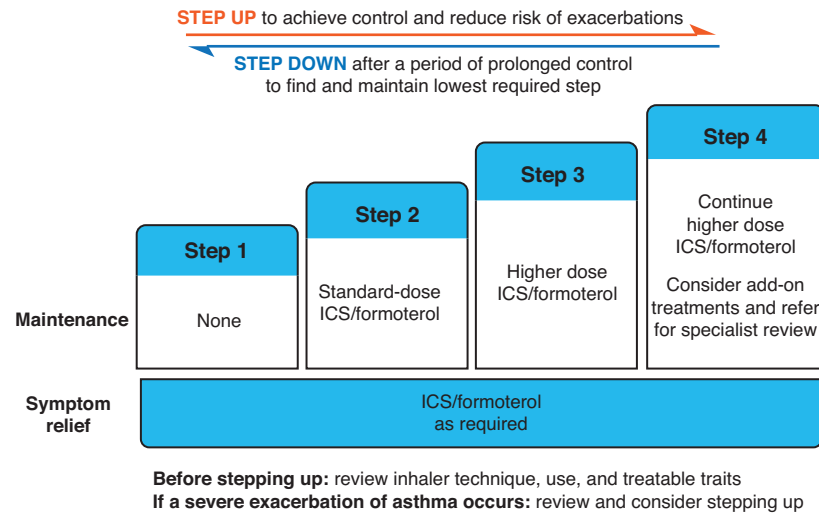
and
University of Otago Wellington,
Wellington New Zealand

Ian D. Pavord, F.Med.Sci.
University of Oxford,
Oxford, United Kingdom

ORCID IDs: 0000-0003-0337-406X (R.B.); 0000-0002-0317-0641 (P.B.); 0000-0003-2062-7225 (L.H.); 0000-0001-5327-3027 (I.B.); 0000-0003-0949-0555 (A.S.); 0000-0003-1254-8287 (C.K.); 0000-0002-0051-9107 (M.W.); 0000-0002-4288-5973 (I.D.P.).

*Corresponding author (e-mail: richard.beasley@mrnz.ac.nz).

A Anti-inflammatory Reliever therapy (AIR) based algorithm using ICS/formoterol



B Traditional SABA reliever therapy based algorithm for asthma management

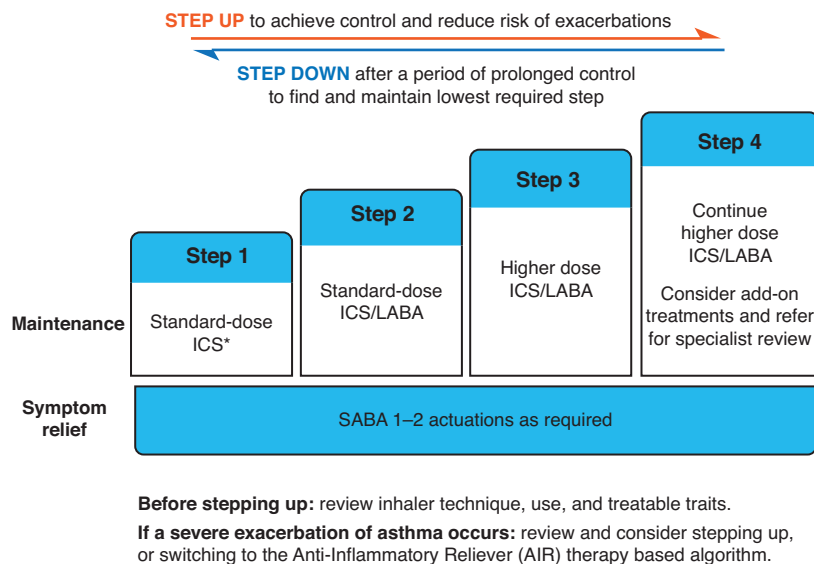


Figure 2. The prototypic algorithms based on (A) antiinflammatory reliever therapy and (B) SABA reliever therapy. *Or standard-dose ICS taken whenever SABA is taken. AIR = antiinflammatory reliever therapy; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; SABA = short-acting β_2 -agonist.

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The Site of Airway Collapse in Sleep Apnea, Its Associations with Disease Severity and Obesity, and Implications for Mechanical Interventions

To the Editor:

The upper airway is composed of various structures. The increase in volume and repetitive collapse of these structures are risk factors for obstructive sleep apnea (OSA). In patients with OSA, the structure or site of obstruction can be identified by using drug-induced sleep endoscopy (DISE), and each obstruction site is believed to increase the severity of OSA. However, some recent studies have reported a negative correlation between the specific type of anatomic obstruction and the apnea–hypopnea index (AHI) (1, 2). These results suggest that not all sites of obstruction identified on DISE influence OSA severity equally. Although the sites of obstruction are commonly considered to represent different phenotypes, no study has formally evaluated the characteristics of these phenotypes in terms of the associations with disease severity, obesity, and implications for mechanical interventions. Therefore, this study aimed to identify the clinical characteristics and expected treatment response according to phenotype labeling using DISE.

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We performed a retrospective review of 637 patients with symptoms of snoring or sleep apnea who underwent polysomnography and DISE from October 2014 to February 2019. Forty-seven patients with incomplete polysomnography or DISE data and three patients with a history of surgery were excluded. Polysomnography was conducted according to American Academy of Sleep Medicine scoring manuals. DISE was performed under propofol or dexmedetomidine while maintaining a bispectral index score between 50 and 70. In addition to supine DISE, simulated maneuvers were used to evaluate the airway status. The results of DISE were assessed on the basis of the VOTE classification (2). The Mann-Whitney *U* test and chi-square and Fisher exact tests were performed to compare the clinical characteristics of patients with and without obstruction. In addition, restricted cubic spline regressions with three knots, adjusting for age, sex, body mass index (BMI), and AHI, were performed to analyze associations between the probability of observing obstruction at each site and AHI (Figure 1). The institutional review board of the Chonnam National University Hospital approved this study protocol (institutional review board number CNUH-2020-282).

Anatomic phenotypes showed varying associations with an increased AHI or an increased BMI (Figure 1). With an increasing AHI, there was an increased probability of observing a velum ($P < 0.001$), oropharynx ($P < 0.001$), or tongue base ($P = 0.001$) obstruction but no increased probability of epiglottic obstruction. However, epiglottis collapse showed no association with the AHI ($P = 0.154$). BMI trends also varied according to the site. Velum and oropharyngeal obstructions were positively correlated with the BMI ($P = 0.024$ and $P < 0.001$), but tongue base ($P < 0.001$) and epiglottis ($P = 0.001$) obstructions were negatively correlated with the BMI.

Patients with velum obstruction showed the most clinical characteristics consistent with OSA. Velum obstruction was positively correlated with the AHI and BMI (Figure 1). In addition, compared with obstructions at other sites, velum obstruction showed male predominance (71.2% vs. 84.6%; $P = 0.001$) and an association with older age (34.7 ± 15.9 vs. 48.2 ± 14.9 ; $P < 0.001$). Considering the highest incidence of velum obstruction (79%; Table 1) in our study participants, velum obstruction may be a representative clinical characteristic of OSA.

Patients with oropharyngeal collapse showed clinical characteristics that were different from those with velum obstruction. Age and sex did not affect oropharyngeal obstruction. Most factors that affected oropharyngeal obstruction in our study were obesity-related, such as the BMI, underlying disease, and lower minimum oxygen saturation. In addition, previous studies showed that obesity was closely related to anatomic factors that cause narrowing of the oropharyngeal lateral wall (3), such as parapharyngeal fat volume (4), lateral pharyngeal muscle thickness, and lateral pharyngeal fat volume (3, 5). Therefore, our findings provide clear support for the notion that oropharyngeal (lateral wall) collapse is influenced by obesity.

In contrast, patients with tongue base obstruction and epiglottis collapse showed different clinical characteristics. The AHI was positively correlated with tongue base obstruction (Figure 1). However, patients with tongue base obstruction had a lower BMI in our study, which contradicts the notion that increased tongue volume is a risk factor for OSA (6). However, this observation is in concordance with findings from a previous study involving phenotype labeling using DISE (1). The study also showed that the patient with tongue base collapse