



# ICS-formoterol reliever therapy stepwise treatment algorithm for adult asthma

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A practical “anti-inflammatory reliever therapy”-based algorithm based on the GINA 2019 update is presented, together with a prototype action plan to facilitate its implementation. <http://bit.ly/33C2s5u>

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## Introduction

A stepwise approach to the pharmacological treatment of asthma is a key feature of current asthma guidelines [1–4]. Through algorithms, treatment intensity is “stepped up” to obtain asthma control and reduce the risk of exacerbations, and “stepped down” after a period of prolonged control and absence of exacerbations. Traditional algorithms advocated short-acting  $\beta_2$ -agonist (SABA) reliever therapy for all levels of severity, initially as sole therapy at Step 1, together with maintenance “low dose” inhaled corticosteroids (ICS) at Step 2, with maintenance ICS/long-acting  $\beta_2$ -agonist (LABA) at “low”, “moderate” or “high” doses at Steps 3 and 4, and finally with “add-on” therapies at Step 5.

In a paradigm shift in the stepwise approach, the 2019 update of the GINA guidelines now recommends ICS/formoterol reliever therapy as the preferred reliever option across all steps of the treatment algorithm [5]. This proposition is based on strong evidence that ICS/formoterol reliever therapy is more effective and safer than SABA reliever therapy for all levels of asthma severity [6–9], as summarised in figure 1. ICS/formoterol reliever therapy can be defined as “anti-inflammatory reliever therapy”, a terminology that probably also applies to combined ICS/SABA reliever therapy, which is more effective at reducing exacerbations than SABA reliever therapy alone [10].

This high-quality evidence has led to recommendations that SABA reliever therapy be replaced by ICS/formoterol reliever therapy in adults with asthma [11–14]. However, for this fundamental change in practice to occur, a practical stepwise treatment algorithm incorporating ICS/formoterol reliever therapy is now needed. The treatment steps for such a prototype anti-inflammatory reliever therapy algorithm are relatively straightforward (figure 2), if based on the clinical trial programmes of budesonide/formoterol reliever therapy regimens, which contribute almost all the evidence of the efficacy and safety of anti-inflammatory reliever therapy, across the spectrum of asthma severity.

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Traditional algorithm using SABA reliever therapy			AIR algorithm			AIR <i>versus</i> traditional risk of severe exacerbations (95% CI)
Step	Maintenance	Reliever	Step	Maintenance	Reliever	
1		SABA	1		B/F	0.36 [0.27–0.49] [6]
1		SABA	1		B/F	0.40 [0.18–0.86] [7]
2	Low dose ICS	SABA	1		B/F	0.83 [0.59–1.16] [6]
2	Low dose ICS	SABA	1		B/F	0.97 [0.78–1.20] [15]
2	Low dose ICS	SABA	1		B/F	0.44 [0.20–0.96] [7]
2	Low dose ICS	SABA	1		B/F	0.69 [0.48–1.00] [16]
2	Low dose ICS	SABA	2	Low dose B/F	B/F	0.24 [0.13–0.42] [17]
3	Medium dose ICS	SABA	2	Low dose B/F	B/F	0.54 [0.44–0.66] [18]
3	Medium dose ICS	SABA	2	Low dose B/F	B/F	0.55 [0.46–0.66] [19]
3	Low dose ICS/LABA	SABA	2	Low dose B/F	B/F	0.47 [0.39–0.57] [18]
3	Low dose ICS/LABA	SABA	2	Low dose B/F	B/F	0.52 [0.44–0.62] [21]
3	Low dose ICS/LABA	SABA	2	Low dose B/F	B/F	0.70 [0.57–0.85] [22]
3	Low dose ICS/LABA	SABA	2	Low dose BDP/F	BDP/F	0.66 [0.55–0.80] [23]
4	Medium dose ICS/LABA	SABA	2	Low dose B/F	B/F	0.81 [0.61–1.09] [24]
4	Medium dose ICS/LABA	SABA	2	Low dose B/F	B/F	0.61 [0.49–0.76] [25]
4	Medium dose ICS/LABA	SABA	2	Low dose B/F	B/F	0.72 [0.57–0.90] [25]
4	Medium dose ICS/LABA	SABA	3	Medium dose B/F	B/F	0.54 [0.36–0.82] [27]
4	Medium dose ICS/LABA	SABA	3	Medium dose B/F	B/F	0.77 [0.61–0.97] [28]
5	High dose ICS/LABA	SABA	3	Medium dose B/F	B/F	0.79 [0.63–0.99] [29]

FIGURE 1 Traditional treatment steps using short-acting  $\beta_2$ -agonist (SABA) reliever therapy *versus* anti-inflammatory reliever (AIR) treatment steps and risk of severe exacerbations in published randomised controlled trials. ICS: inhaled corticosteroid; LABA: long-acting  $\beta_2$ -agonist. The following studies contained inclusion criteria that required a history of an exacerbation in the 12 months prior to randomisation [18, 19, 21–23, 25, 27–29]. The risk of severe exacerbation (AIR *versus* traditional algorithm) was reported as relative rate [6, 15, 16, 19, 21, 23–25, 27, 29], relative risk [7, 17, 28] and hazard ratio [18, 22], respectively. Studies prescribed reliever therapy as follows; budesonide/formoterol (B/F) 200/6  $\mu\text{g}$ , one actuation as required for relief of symptoms [6, 7, 15, 16, 19, 21, 22, 24, 25, 27–29]; B/F 100/6  $\mu\text{g}$ , one actuation as required for relief of symptoms [17, 18]; ultrafine beclometasone dipropionate/formoterol 100/6  $\mu\text{g}$  (BDP/F), one actuation as required for relief of symptoms [23].

### Step 1

Step 1 in the anti-inflammatory reliever algorithm is budesonide/formoterol 200/6  $\mu\text{g}$  one actuation as-needed *via* the Turbuhaler as reliever monotherapy in mild asthma. This is superior to the traditional Step 1 treatment, either as-needed SABA reliever monotherapy with terbutaline [6] or salbutamol [7], in reducing severe exacerbation risk and improving asthma control (figure 1). The clinical trial evidence also shows that the budesonide/formoterol reliever monotherapy regimen reduces airways inflammation (as measured by exhaled nitric oxide fraction), thereby confirming its designation as an “anti-inflammatory reliever therapy” [7].

Step 1 treatment with budesonide/formoterol reliever therapy results in a similar [6, 15] or greater reduction [7, 16] in severe exacerbation risk than traditional Step 2 maintenance “low dose” ICS and SABA reliever therapy, with no clinically important difference in asthma control figure 1).

### Step 2

Step 2 in the anti-inflammatory reliever therapy algorithm is “low dose” budesonide/formoterol maintenance and reliever therapy, which is superior to both the traditional Step 2 treatment of maintenance “low dose” ICS together with SABA reliever therapy [17], and one of the alternative Step 3 treatment options, maintenance “medium/high dose” ICS together with SABA reliever therapy (figure 1) [18, 19]. Four dosing options have supportive evidence from clinical trials: budesonide/formoterol 200/6  $\mu\text{g}$  Turbuhaler two actuations once daily as maintenance together with one actuation as-needed for symptom relief [19], budesonide/formoterol 200/6  $\mu\text{g}$  one actuation twice daily as maintenance together with one

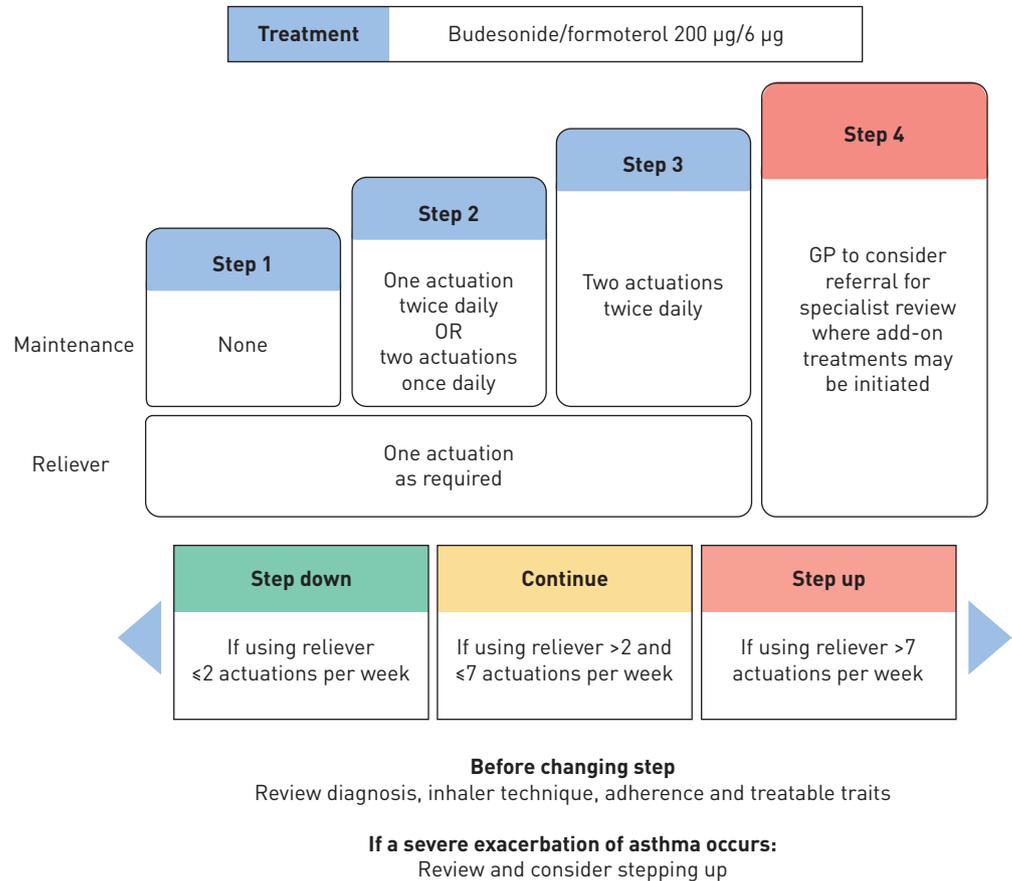


FIGURE 2 Prototype anti-inflammatory reliever therapy algorithm for clinic-based review in adult asthma based on budesonide/formoterol 200/6 µg Turbuhaler. Alternative cut points could be used to guide transition between steps (see text). GP: general practitioner.

actuation as-needed [20–22], budesonide/formoterol 100/6 µg Turbuhaler two actuations once daily as maintenance together with one actuation as needed [17], and budesonide/formoterol 100/6 µg Turbuhaler one actuation twice daily as maintenance together with one actuation as-needed [18]. It may be preferable to use the budesonide/formoterol 200/6 µg Turbuhaler, as this reduces treatment complexity and enables standardisation of the 200/6 µg dose per actuation across the different steps of this proposed algorithm.

The “low dose” budesonide/formoterol maintenance and reliever therapy regimen is more effective than the traditional Step 3 treatment, maintenance “low dose” ICS/LABA together with SABA reliever therapy (figure 1) [18, 21, 22]. This is consistent with clinical trial evidence that “low dose” beclomethasone/formoterol maintenance and reliever regimen is superior to “low dose” beclomethasone/formoterol together with SABA reliever therapy [23]. The “low dose” budesonide/formoterol maintenance and reliever therapy regimen is also more effective than the traditional Step 4 treatment, “medium dose” maintenance ICS/LABA together with SABA reliever therapy, in reducing severe exacerbation risk (figure 1) [24, 25].

In considering this evidence of comparative efficacy, it is necessary to recognise that in six of the eight studies of anti-inflammatory reliever therapy at Step 2, the studies’ inclusion criteria required a history of an exacerbation in the 12 months prior to randomisation, thereby enhancing the power of the study, although reducing the generalisability of the findings to patients at lower levels of exacerbation risk.

In summary, Step 2 of the anti-inflammatory reliever therapy algorithm, “low dose” budesonide/formoterol maintenance and reliever therapy is more effective than the traditional ICS and ICS/LABA regimens incorporating SABA reliever therapy at Steps 2, 3 and part of 4 in traditional guidelines. This is consistent with the proposition that from Step 2 to 4, the choice of reliever therapy is a major determinant of therapeutic efficacy in adult asthma [26].

### Step 3

Step 3 of the anti-inflammatory reliever therapy algorithm is “medium dose” budesonide/formoterol maintenance and reliever therapy, which is more effective than the traditional Step 4 treatment,

maintenance “medium dose” ICS/LABA together with SABA reliever therapy (figure 1) [27, 28]. In studies of this regimen, which required a history of an exacerbation in the 12 months prior to randomisation, budesonide/formoterol 200/6 µg has been self-administered from both a Turbuhaler and a pressurised metered dose inhaler (pMDI) device. However, as budesonide/formoterol pMDI devices have not yet been assessed at the other steps in the algorithm, they do not represent an option for use in an algorithm which incorporates the same budesonide/formoterol 200/6 µg inhaler device across the spectrum of asthma severity. Further research of the budesonide/formoterol 200/6 µg and 100/3 µg pMDI products is a priority to provide the evidence base required for this option, not least because most patients are used to taking SABA reliever therapy through a pMDI.

The “medium dose” budesonide/formoterol maintenance and reliever regimen is also more effective than “high dose” ICS/LABA together with SABA reliever therapy, which is now designated as one of the Step 5 treatment options (figure 1) [29]. This trial evidence is based on comparison with both budesonide/formoterol and fluticasone propionate/salmeterol at about double the equivalent maintenance ICS dose, together with SABA reliever therapy. This indicates that the greater efficacy is due to budesonide/formoterol compared with SABA use as reliever therapy, rather than the specific ICS/LABA product used for maintenance therapy.

#### Step 4

Step 4 of the anti-inflammatory reliever therapy-based algorithm would be similar to Step 5 of the algorithms represented in traditional guidelines, in which add-on therapies such as long acting muscarinic antagonists, leukotriene receptor antagonists, macrolides and biologics are considered, together with specialist review.

In summary, the three treatment levels based on a single budesonide/formoterol 200/6 µg Turbuhaler taken as a reliever, either as monotherapy or together with “low” or “medium” dose maintenance budesonide/formoterol therapy are superior to the corresponding five treatment steps based on SABA reliever therapy, either as monotherapy, or together with ICS or ICS/LABA maintenance therapy.

#### Transition between steps

An important issue is how to enable patients to move between the treatment steps recommended by the anti-inflammatory reliever therapy algorithm. A simple step up/step down system could be used, based on the frequency of reliever use over a period of a month, and whether there has been a recent severe exacerbation. The point of transition from as-needed reliever to regular maintenance and reliever use may not need to be standardised, and could be based on patient and prescriber preferences.

High  $\beta_2$ -agonist rescue medication use is a marker of poor asthma control and exacerbation risk [30, 31], both of which respond to higher doses of regular ICS therapy [32]. For this reason, if a patient uses their budesonide/formoterol Turbuhaler as-needed for relief on average more than seven actuations per week, then the logical step up approach would be to add two additional daily maintenance actuations to the maintenance regimen, with the patient thereby moving up a step, however, not beyond Step 3. For patients who use their budesonide/formoterol as reliever on average between two and seven actuations per week, then their maintenance dose could be left unchanged. For patients with budesonide/formoterol reliever use on average no more than two occasions per week, then their maintenance dose could be reduced by a step, but not beyond Step 1. An alternative, less conservative approach would be to use cut points of budesonide-formoterol reliever use of two or more actuations per day to step up; around once a day on average to remain at the same level, and less than once a day on average to step down.

A severe exacerbation should prompt medical review for consideration of an increase in treatment level, as this event would be associated with a marked increase in the risk of future severe exacerbations [30, 31, 33, 34]. This transition system would result in treatment defined by a specific step being taken for the period between clinic reviews, or for periods of at least a month when self-managed by the patient.

#### Implementation

Through the use of asthma action plans, a prompt and smooth transition between the levels of treatment could be achieved, which after education by health professionals may then be undertaken without clinic-based medical review. A prototype action plan that has been developed from the action plans used in studies of budesonide/formoterol reliever therapy is proposed for use by patients in their self-management (figure 3) [7, 27]. After the patient becomes familiar with the system, patients would then be able to transition between steps themselves, without requirement to seek clinical review prior to treatment step decisions.

# AIR adult asthma action plan

Name: \_\_\_\_\_ Doctor: \_\_\_\_\_

Date of plan: \_\_\_\_\_ Doctor phone: \_\_\_\_\_

SYMBICORT (Budesonide / Formoterol 200ug/6ug)

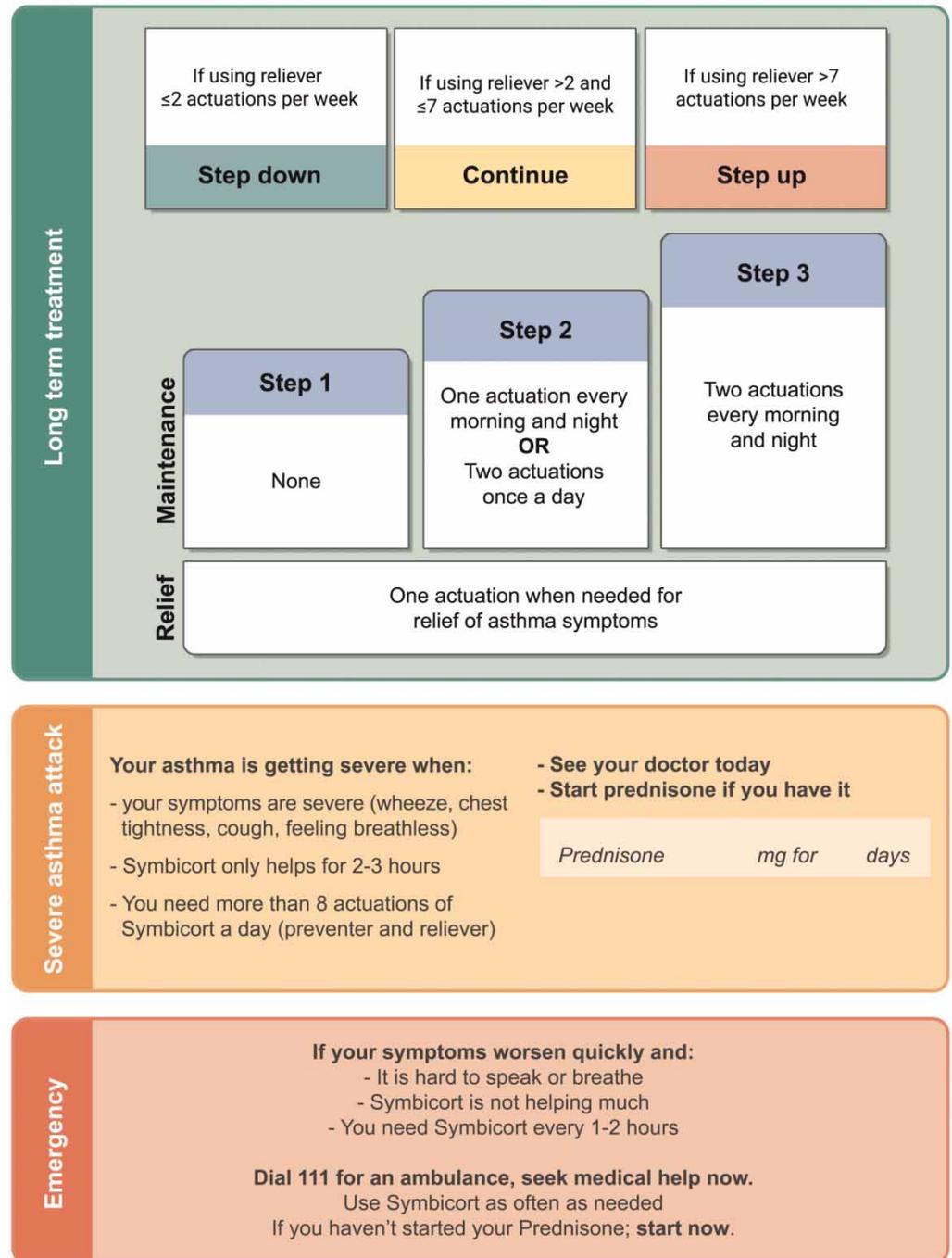


FIGURE 3 Prototype adult asthma action plan for the anti-inflammatory reliever therapy stepwise treatment algorithm developed from the action plans used in the studies of budesonide/formoterol reliever therapy that demonstrated efficacy and safety of this regimen [7, 25]. On the reverse side of the plan additional information and guidance can be provided, but not limited to inhaler and spacer technique, medication use and the frequency of recommended medical review.

### Concluding comments

The proposed anti-inflammatory ICS/formoterol reliever therapy-based algorithm is based on budesonide/formoterol, due to the extensive evidence of its efficacy and safety when used in this way, across the range

of asthma severity in adult asthma. However, it seems likely that the algorithm could be based on other ICS/formoterol products, such as beclometasone dipropionate/formoterol, or ICS/SABA products, such as beclometasone dipropionate/salbutamol, for which there is evidence of efficacy at one step, but not across the range of asthma severity, as would be required for their incorporation in an algorithm [12, 26].

This novel anti-inflammatory reliever therapy-based algorithm and associated action plans will need assessment, in particular by comparison with the traditional SABA reliever therapy-based algorithms, covering efficacy, safety, steroid burden, patient preference and economic cost. This would determine whether the proposed anti-inflammatory reliever therapy algorithm is superior to the traditional algorithms, as is suggested by comparisons of the different regimens at the individual steps of the algorithms, and its place in asthma management in countries in which budesonide/formoterol products are available.

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