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Review paper

New guidelines for the treatment of seasonal allergic rhinitis

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Abstract

The paper discusses the classification and forms of allergic rhinitis with a special focus on seasonal allergic rhinitis (SAR). The general principles of SAR management are presented, including the role of nasal glucocorticoids, nasal and oral antihistamines, and antileukotrienes. Based on the latest guidelines, the current rules for the selection of drugs in the therapy of SAR are given, paying special attention to the initial treatment. The aim of the paper is to present updated guidelines for the pharmacological management of patients with seasonal allergic rhinitis.

Key words: seasonal allergic rhinitis, children, adults, antihistamines, nasal glucocorticoids, antileukotrienes.

Definition and forms of allergic rhinitis

Allergic rhinitis (AR) is an inflammatory process of the nasal mucosa, typically IgE-mediated, elicited by environmental allergens and characterized by the presence of inflammatory cells within the mucosa and submucosa [1]. The course of the disease involves one or more of the symptoms enumerated below, persisting for at least one hour a day for at least two consecutive days, which are reversible spontaneously or with treatment. The symptoms include nasal discharge, nasal itching, sneezing and nasal obstruction [2, 3].

The disease is a serious public health problem in a number of countries, including Poland where approximately 9 million people are affected by various forms of AR [4]. Allergic rhinitis has a profound negative impact on the quality of life of patients and their families (in the case of children with AR). It is also a major cause of school and work absenteeism [5-7]. Consequently, it is vital to ensure timely and correct diagnosis, and implement appropriate management based on the latest international or national guidelines.

For many years there have been attempts to systematize various forms of AR based on a number of criteria. The current classifications of AR take into account the following criteria:

1) *allergen causing symptoms* (aetiological classification; the oldest and still useful in the clinical setting, popular particularly in the USA),
2) *duration of symptoms* (clinical classification easy to implement in practice, with significant implications for therapy),
3) *severity of clinical symptoms* reported by the patient, including AR-related quality of life (clinical classification easy to implement in clinical practice, easily understandable to patients, with significant implications for therapy),
4) *disease pathophysiology* (pathophysiological classification with, as yet, limited use in clinical practice).

According to the first criterion, partially including the aetiology of the disease, AR is divided into seasonal (SAR), perennial (PAR) and episodic (EAR) types [8]. Seasonal allergic rhinitis (SAR) develops only during specific periods of the year (corresponding to the pollination of wind-pollinated plants or mould sporulation). Perennial allergic rhinitis (PAR) occurs when the condition is triggered by allergens found in the patient's environment at concentrations sufficient to induce symptoms of the disease all year round. The triggers include house dust mites, pet fur, cockroaches and mould in the Central Europe or wind-pollinated plant pollen in the tropical zone. Episodic allergic rhinitis (EAR) is caused by exposure to a specific airborne allergen on a sporadic and short-term basis [9].

Based on the second criterion, i.e. duration, AR is classified [10] into intermittent (INT) and persistent (PER) types (Figure 1). Intermittent allergic rhinitis is defined by

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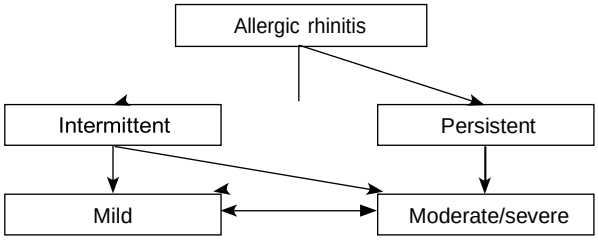

Figure 1. Classification of AR and relationships between different AR forms

symptom duration of less than 4 days per week or less than a month per year, and PER allergic rhinitis refers to the presence of symptoms for ≥ 4 days per week and ≥ 1 month per year.

According to the third criterion, AR is classified as either mild or moderate/severe (original ARIA classification, oARIA), depending on the impact of the disease on the following quality-of-life measures [3] (Figure 1): a) daily activities and sport, b) school/work attendance, c) sleep, and d) need of therapy, as reported by the patient.

In mild AR, there is no impact on the quality-of-life aspects listed above. In moderate/severe AR, an adverse effect on one or more of the above items is present. On account of the high heterogeneity observed in the group of patients with this form of the disease, a more detailed classification has been proposed, consisting of three levels of AR severity [11]: mild, moderate and severe. In contrast to oARIA, the revised system is referred to as modified ARIA (mARIA) classification. The mild form is defined in the same manner as in oARIA. In the moderate form, the disease affects the presence of one, two or three out of four (a, b, c, d) of the above-mentioned elements of AR severity assessment. In the severe form, impact of the disease is seen in all four elements.

Based on the fourth criterion listed above, i.e. pathophysiology, AR is divided into IgE-mediated and non-IgE-mediated types. The former is much more common (> 90% cases), and the latter probably involves IgG antibodies, T lymphocytes and/or eosinophils [12]. Muraro *et al.* have recently proposed a new classification of IgE-mediated AR endotypes [13]. However, its implementation in daily practice is still in its early stages (patients require detailed immunological assessment), just like the potential variation in therapy resulting from the classification.

Both intermittent (INT) and persistent (PER) AR may have a mild or moderate/severe clinical course and different forms of the disease may pass into one another (effect of evolution of the disease and/or therapy) (Figure 1). Some patients are affected by the so-called mixed rhinitis in which AR coexists with non-allergic rhinitis (44-87% of patients with AR) [14].

Seasonal AR may have an intermittent course, for example in Poland some patients are only allergic to alder pollen. It may also take a persistent form as in patients with grass pollen allergy (Table 1).

Seasonal allergic rhinitis and main disease-triggering allergens

A few years ago, the results of the ECAP study investigating SAR prevalence in children and adults in Poland were published [4, 15]. Table 2 lists data on the prevalence of SAR in selected Polish cities based on medical diagnosis of the disease [4].

The prevalence of SAR varied from 6.1% to 20.8% in the group of younger children, from 7.6% to 29.0% in the group of older children and from 8.8% to 28.9% in adults. The disease was more prevalent in boys/men than in girls/women. The data show that the condition is the most common inflammatory respiratory disease.

The dominant allergens triggering SAR in Poland include, in order of frequency, pollen of grasses/cereals,

Table 1. Pollination periods of wind-pollinated plants in Poland (approximate data unified for the country as a whole; differences for the beginning and/or the end of the pollination period between climatic regions in Poland span about 3 to 4 weeks) [18]

Plants	Alder, hazel	Birch	Oak, beech, willow, ash, poplar	Grasses, cereals	Goosefoot, plantain, mugwort
Month	I–III/Jan–Mar	IV–V/Apr–May	IV–V/Apr–May	V–VII/May–July	VII–IX/July–Sep

Table 2. Prevalence of seasonal AR in Poland (% population) in children and adults based on medical diagnosis

City	Children aged 6–7 years (%)	Children aged 13–14 years (%)	Adults aged 20–44 years (%)
Warsaw	20.8	31.1	27.4
Krakow	9.2	12.2	9.6
Wroclaw	6.1	7.6	8.8
Poznan	17.0	29.0	28.9
Gdansk	15.3	22.8	16.8
Bialystok	10.7	15.5	12.5

birch, mugwort, alder and hazel, followed by other pollens (nettle, goosefoot, broadleaf plantain and ragweed). The sequence in which different airborne pollens occur in Poland is quite characteristic [16]. The plant pollination season usually begins in the first decade of February, when hazel and alder pollen is detected in the air. In favourable weather conditions, however, the two plant pollen allergens are already airborne in mid-January. Birch, whose antigens are the most common cause of AR in the spring, begins pollinating in April. Other deciduous trees including ash, beech, hornbeam and poplar, usually produce pollen in Poland until mid-May, and are less clinically significant than birch. Exposure to grass pollen antigens, which are the most common cause of SAR in Poland, is the greatest at the end of May, in June and July. In August and September, the main airborne pollens are herbaceous plants (weeds), primarily mugwort, goosefoot and plantain. Allergy to mugwort pollen allergens is the third most common (after grass and birch pollen) cause of SAR, and the allergens appear in August and September. The above data are listed in Table 1 [17].

It must be noted that SAR symptoms very commonly (in 60-90% of cases) coexist with symptoms of allergic conjunctivitis such as burning and itching of the eyes, redness and increased lacrimation. The condition is referred to as allergic rhinoconjunctivitis.

Rules of seasonal allergic rhinitis management: drug categories

For many years, the algorithm for the treatment of patients with SAR has combined four basic modalities which often require concurrent application [3, 18-20]:

1) education of patients (in children also their caregivers),
2) avoidance of allergens and irritants (possible in SAR),
3) pharmacotherapy (all therapeutic options),
4) allergen immunotherapy (sublingual or subcutaneous, effective particularly in SAR).

Seasonal allergic rhinitis pharmacotherapy is based on different drug categories, either used in monotherapy or, in some patients, in combined regimens according to the criteria included in currently valid diagnostic and therapeutic consensus recommendations. The most important drug categories include:

- glucocorticoids (GC): intranasal – GCin, oral – GCpo,
- H1 receptor antagonists (second-generation H1-antihistamines – AH) (oral – AHpo, intranasal – AHin),
- antileukotrienes (ALTR) (in children mainly montelukast),
- ipratropium bromide (intranasal),
- α-sympathomimetics (intranasal, oral),
- saline solutions (intranasal),
- anti-IgE antibodies (subcutaneous),
- cromones (intranasal).

The effect of different drug categories on symptoms of SAR and ocular manifestations frequently accompanying the disease varies greatly, as shown in Table 3 [3, 8, 21-25].

Current principles of drug selection in seasonal allergic rhinitis

The selection of pharmacological options suitable for a particular patient depends to the largest extent on the form and clinical severity of SAR, patient's age (approved drug indications), drug availability on the market, price, and patient acceptance and satisfaction with a particular management modality [8, 26, 27]. The pharmacother-

Table 3. Drug categories used in the therapy of SAR and their effect on nasal and ocular symptoms under normal exposure

Drug category	SAR symptoms and ocular symptoms					
	Sneezing	Itching	Watery discharge	Nasal blockage	Smell disorders	Ocular symptoms
Antihistamines (p.o.)	++	++	++	+/–	–	++
Antihistamines (i.n.)	++	+++	++	+	–	–
Ipratropium bromide (i.n.)	–	–	+++	–	–	–
α-sympathomimetics (i.n.)	–	–	–	++	+/–	–
α-sympathomimetics (p.o.)	–	–	–	+	–	+/–
Antileukotrienes (p.o.)	+	+	++	++	+	+
Glucocorticoids (i.n.)	+++	+++	+++	++	+	++
Glucocorticoids (p.o.)	+++	++	+++	++	+	+++
Anti-IgE (s.c.)	++	++	++	++	nd	++
Saline solutions (i.n.)	+	+	+	nd	–	–
Cromones (i.n.)	+	+	+	+/–	–	–

i.n. – intranasal drugs, p.o. – oral drugs, s.c. – subcutaneous drugs, (–) – no effect, (+/–) – uncertain effect, (+) – some effect, (++) – strong effect, (+++) – very strong effect, (nd) – no data.

apy of SAR is gradable. If the disease exacerbates, the treatment can be intensified, usually by adding another medication (step-up approach). Conversely, if there is an improvement in symptom control, the therapy is reduced, typically by discontinuing 1 or 2 drugs (step-down approach) [27].

In 2015, a study entitled "MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): The new generation guideline implementation" was published, providing a very important resource for patients [28]. The study proposes a mobile phone application, MACVIA-ARIA, which allows patients to easily keep track of a number of parameters in the Visual Analogue Scale (VAS), including general well-being, nasal symptoms, conjunctival (ocular) symptoms, asthma symptoms and impact of symptoms on work productivity. VAS is a 10-centimetre scale which can be used by the patient at home (or by the physician during the patient's visit) to mark the severity of symptoms (from zero – no symptoms, to 10 – most severe symptoms). VAS is a sensitive and precise tool for the assessment of AR symptoms and correlates well with the patients' quality of life [29]. The scale is particularly useful in patients with SAR [30]. Objective recording of SAR symptoms makes it possible to select a more effective drug therapy and enables adjustments by the physician but also by the pharmacist and/or patients themselves [31, 32].

The current therapeutic algorithm for AR (including SAR) proposed in the MACVIA-ARIA guidelines for previously untreated (first-line) patients ≥ 12 years of age recommends one of the following options [20]: AHpo or AHin, GCin, ALTR (montelukast) and combination therapy: GCin + AHin (azelastine).

In patients having AR symptoms with a VAS score of < 5, the guidelines recommend selecting one drug from the options listed above (without specifying which one). The recommended management for patients with more severe symptoms (VAS ≥ 5) is:

1) in patients with symptoms indicative of INT AR, the management is the same as in patients with VAS < 5;
2) in patients with symptoms indicative of PER AR, the recommended therapy is GCin or GCin + azelastine.

Further therapy depends on the patient's response to the initial treatment (daily VAS score assessment and, if necessary, modification of management after 48-72 h).

In patients with AR previously treated with one of the four available therapeutic options (AHpo/AHin or GCin or ALTR (montelukast) or combination treatment with GCin + AHin (azelastine)) and a VAS score of < 5, the recommended management is:

1) in cases of INT AR or absence of allergen exposure – reduce the treatment (step-down approach) or discontinue the therapy;
2) in cases of PER AR or presence of allergen exposure – maintain the treatment or intensify the therapy (step-up approach).

Further therapy depends on the patient's response to the initial treatment (daily VAS score assessment and, if necessary, modification of management after 48-72 h).

In patients with a current VAS score of ≥ 5, regardless of AR type, the treatment should be stepped up by adding GCin or a combination of GCin + AHin (azelastine). Further therapy depends on the patient's response to the initial treatment (daily VAS score assessment and, if necessary, modification of management after 7 days). The current principles of patient management in AR (without differentiation into SAR and PER AR) have recently been summarized by Bousquet *et al.* [20]. The process of selecting a suitable therapeutic option should be guided by the following principles:

- AHpo or AHin are less effective than GCin for the control of all symptoms of allergic rhinitis.
- ALTR (montelukast) is usually considered less effective than AHpo.
- There are no differences in the assessed efficacy of AHin and AHpo, so no definite recommendations have yet been made.
- Combined intranasal fluticasone propionate (FP) and azelastine (AZL) in a single intranasal device is more clinically effective than monotherapy, and it is indicated for patients when monotherapy with either AHin or GCin is considered inadequate.
- AHin and GCin are similarly effective for the treatment of ocular symptoms. However, the combination of FP and AZL is more effective than FP alone.
- Most studies show that combinations of AHpo and GCin or ALTR (montelukast or another drug from this category) and GCin are not more effective than GCin in monotherapy.
- Intraocular AH or cromones are effective for the treatment of ocular symptoms caused by allergic conjunctivitis.
- GCin are clinically effective after a few days of treatment, whereas AHin or combined intranasal FP and AZL produce a much more rapid clinical effect.
- First-generation AH should not be used in AR.
- Further studies are necessary in preschool age children in order to develop strong therapeutic recommendations, however recent research has demonstrated the efficacy of AHpo.

As mentioned above, the management algorithms for SAR proposed to date have not provided clear recommendations for selecting a therapeutic option for the initial therapy out of the four modalities listed above, especially based on the recognized GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluations) [33, 34]. The problem has recently been taken up by a team of the most prominent American experts, and conclusions of their GRADE-based study were published in December 2017 [35]. The authors of the study formulated three key questions having practical significance and pertaining to the initial patient

management in moderate/severe SAR (in previously untreated patients):

1. Is there any clinical benefit of using a combination of an AHpo and a GCin compared with monotherapy with a GCin in patients who are > 12 years of age?
2. How does montelukast compare with a GCin in terms of clinical efficacy in patients who are ≥ 15 years of age?
3. Is there any clinical benefit of using combination therapy with a AHpo and a GCin compared with monotherapy with either drug in patients who are > 12 years of age?

Three recommendations were formulated in response to the three questions.

Recommendation 1

For the initial treatment of moderate/severe SAR in patients aged 12 years or older, clinicians should routinely prescribe monotherapy with a GCin rather than a combination of a GCin and an AHpo (strength of recommendation: strong).

Authors' own commentary

The recommendation significantly changes the management guidelines recommended to date, in whichthe treatment with a GCin and an AHpo was regarded as a "gold standard" in the therapy of more severe SAR. However, the treatment based on the two drug types fails to produce clinically significant additional benefits over a GCin in monotherapy and it is more expensive than the latter. Furthermore, since the combination is not superior to a GCin, it will encourage the shift to a GCin in patients who show no clinical benefit from treatment with an AHpo alone (instead of adding a GCin to an AHpo).

Recommendation 2

For the initial treatment of moderate/severe SAR in patients aged 15 years or older, clinicians should prescribe monotherapy with a GCin over montelukast (strength of recommendation: strong).

Authors' own commentary

The recommendation only slightly changes the current SAR management guidelines. Montelukast has been known for many years to be a markedly weaker anti-inflammatory drug than GCin, which is stressed in the 2016 study by Bousqet *et al.* [20]. The role of montelukast in the therapy of SAR seems to have been decreasing markedly in recent years. In practical terms, the drug may be effective only in patients with SAR coexisting with asthma during the pollination season (which is consistent with the Polish SPC of the drug) [36]. Montelukast can also have applications in a small group of patients with SAR who are intolerant of intranasal drugs [37].

Recommendation 3

For the initial treatment of moderate/severe SAR in patients aged 12 years or older, clinicians may recommend the combination of a GCin and AHin (strength of recommendation: weak).

Authors' own commentary

Only one GCin and AHin combination is available in Poland. It is the product called Dymista® containing an original formulation of FP with AZL in a single intranasal device. According to the current SPC for the medicinal product, the combination is effective in relieving symptoms of moderate/severe SAR in cases when other AHin or GCin fail to ensure adequate control of disease symptoms [38]. Consequently, the combination seems more appropriate as a second-line therapeutic modality which can be introduced after attempting monotherapy. However, the current therapeutic algorithm for SAR proposed in the MACVIA-ARIA guidelines for patients aged ≥ 12 years includes the AHin and GCin combination as one of the four proposed options of first-line therapy, as mentioned above [20]. Unfortunately, there are still no clear indications which groups of patients would benefit from this therapy as opposed to other therapeutic options in the initial treatment of SAR.

Conclusions

Seasonal allergic rhinitis is triggered by allergens of wind-pollinated plants (tree, grass/cereal and weed/bush pollen). In the initial treatment of moderate/severe SAR in previously untreated patients aged 12 years or older, clinicians should routinely prescribe monotherapy with an intranasal glucocorticoid instead of combined therapy with an intranasal glucocorticoid and an oral second-generation antihistamine (strong recommendation) or montelukast in monotherapy (strong recommendation). Another possibility is the combination of an intranasal glucocorticoid with an intranasal antihistamine drug in a single intranasal device (weak recommendation). The above recommendations reduce the role of oral antihistamine drugs and montelukast in this group of patients with SAR.

Conflict of interest

The authors declare no conflict of interest.

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Review article

Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence

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The selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends on many factors. Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines have considerably improved the treatment of allergic rhinitis. However, there is an increasing trend toward use of real-world evidence to inform clinical practice, especially because randomized controlled trials are often limited with regard to the applicability of results. The Contre les Maladies Chroniques pour un Vieillissement Actif (MACVIA) algorithm has proposed an allergic rhinitis treatment by a consensus group. This simple algorithm can be used to step up or step down allergic rhinitis treatment. Next-generation guidelines for the pharmacologic treatment of allergic rhinitis were developed by using existing GRADE-based guidelines for the disease, real-world evidence provided by mobile technology, and additive studies (allergen chamber studies) to refine the MACVIA algorithm. (J Allergy Clin Immunol 2020;145:70-80.)

Key words: Allergic rhinitis, Allergic Rhinitis and Its Impact on Asthma, Grading of Recommendations Assessment, Development and Evaluation, guidelines, real-world evidence

Abbreviations used
ARIA: Allergic Rhinitis and Its Impact on Asthma
GRADE: Grading of Recommendations Assessment, Development and Evaluation
ICP: Integrated care pathway
INCS: Intranasal corticosteroid
MACVIA: Contre les Maladies Chroniques pour un Vieillissement Actif
MASK: Mobile Airways Sentinel Network
mHealth: Mobile Health
MPAzeFlu: Azelastine–fluticasone propionate combination
MPR: Medication possession ratio
PDC: Proportion of days covered
RWE: Real-world evidence
VAS: Visual analogue scale
WHO: World Health Organization

Selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends on (1) patient empowerment, preferences, and age; (2) prominent symptoms, symptom severity, and multimorbidity; (3) efficacy and safety of treatment[1]; (4) speed of onset of action of treatment; (5) current treatment; (6) historic response to treatment; (7) effect on sleep and work productivity[2,3]; (8) self-management strategies; and (9) resource use.[4,5]

An algorithm was devised[5] and digitalized[6] to step up or step down allergic rhinitis treatment based on control. However, its

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use varies depending on the availability of medications and resources. Algorithms require testing with real-world evidence (RWE) that includes randomized controlled trials and observational research with real-world data.[7-9]

To evaluate estimates of effects, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology explicitly considers all types of study designs from randomized controlled trials to case reports, although guideline developers often restrict guidelines to randomized controlled trials.[10-12] GRADE also considers evidence on prognosis, diagnosis, values and preferences, acceptability, and feasibility or directness of findings. There is an increasing trend

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FIG 1. Organizations supporting the meeting (Paris; December 3, 2018). *CEmPac*, Centre for Empowering Patients and Communities; *EAACI*, European Academy of Allergy and Clinical Immunology; *EIT Health*, European Institute for Innovation and Technology; *EFA*, European Federation of Allergy and AirwaysDiseases Patients' Associations; *ERS*, European Respiratory Society; *Euforea*, European Forum for Research and Education in Allergy and Airways Diseases; *GA²LEN*, Global Allergy and Asthma European Network; *GARD*, Global Alliance against Chronic Respiratory Diseases (WHO Alliance); *GINA*, Global Initiative for Asthma; *POLLAR*, Impact of Air Pollution in Asthma and Rhinitis; *SFA*, Société française d'Allergologie; *SPLF*, Societé de Pneumologie de Langue Française; *WAO*, World Allergy Organization.

to use real-world data to inform clinical practice, especially because randomized controlled trials are often limited tothe applicability of results.[13] The tradeoff that is madeis one between risk of bias, primarily selection and confounding bias, and applicability. Ideally, both types of evidence are merged.

Guidelines are not sufficiently followed because they are not close enough to patients' needs and probably do not reflect real life. In cluster-randomized trials guideline-driven treatment is more effective than free treatment choice.[14,15] Moreover, guidelines (in rhinitis but also in asthma) have led to a better understanding of the treatment of the disease and havehad an important teaching role that has led to changemanagement.[16]

In addition, there is a need to support transformation of the health care system for integrated care with organizational health literacy.[16,17] During a recent meeting held in Paris (December 3, 2018) for chronic disease care, Mobile Airways Sentinel Network (MASK)[18] and Impact of Air Pollution on Asthma andRhinitis (POLLAR; European Institute for Innovation and Technology–Health [EIT Health]),[19] in collaboration withprofessional and patient organizations in the field of allergy andairway diseases (Fig 1), recommended the evaluation of real-life care pathways (integrated care pathways [ICPs]) centered around the patient with rhinitis and asthma.

During the ICP meeting in Paris, next-generation guidelines for the pharmacologic treatment of allergic rhinitis were developed by using existing GRADE-based guidelines for allergic rhinitis,[5,20-22] RWE provided by randomized controlled trials, real-world data using mobile technology,[23,24] and chamber studies (Fig 2).[5,6,16-20,25-27] These recommendations were used to refine the algorithm for allergic rhinitis treatment proposed by a consensus group.[5]

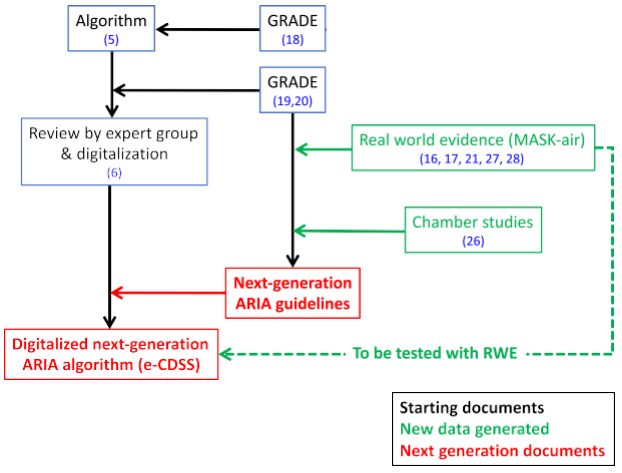

FIG 2. Development of next-generation ARIA guidelines.

The present report describes the process of next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA)–GRADE guidelines for the pharmacologic treatment of allergic rhinitis.

DOCUMENTS CONSIDERED FOR DEVELOPMENT OF ARIA CARE PATHWAYS

Contre les Maladies Chroniques pour un Vieillissement Actif (MACVIA) algorithm proposing a stepwise approach for allergic rhinitis pharmacologic treatment

An algorithm based on the visual analogue scale (VAS)[28] has been devised by the ARIA expert group (1) for selection of pharmacotherapy for patients with allergic rhinitis and (2) to

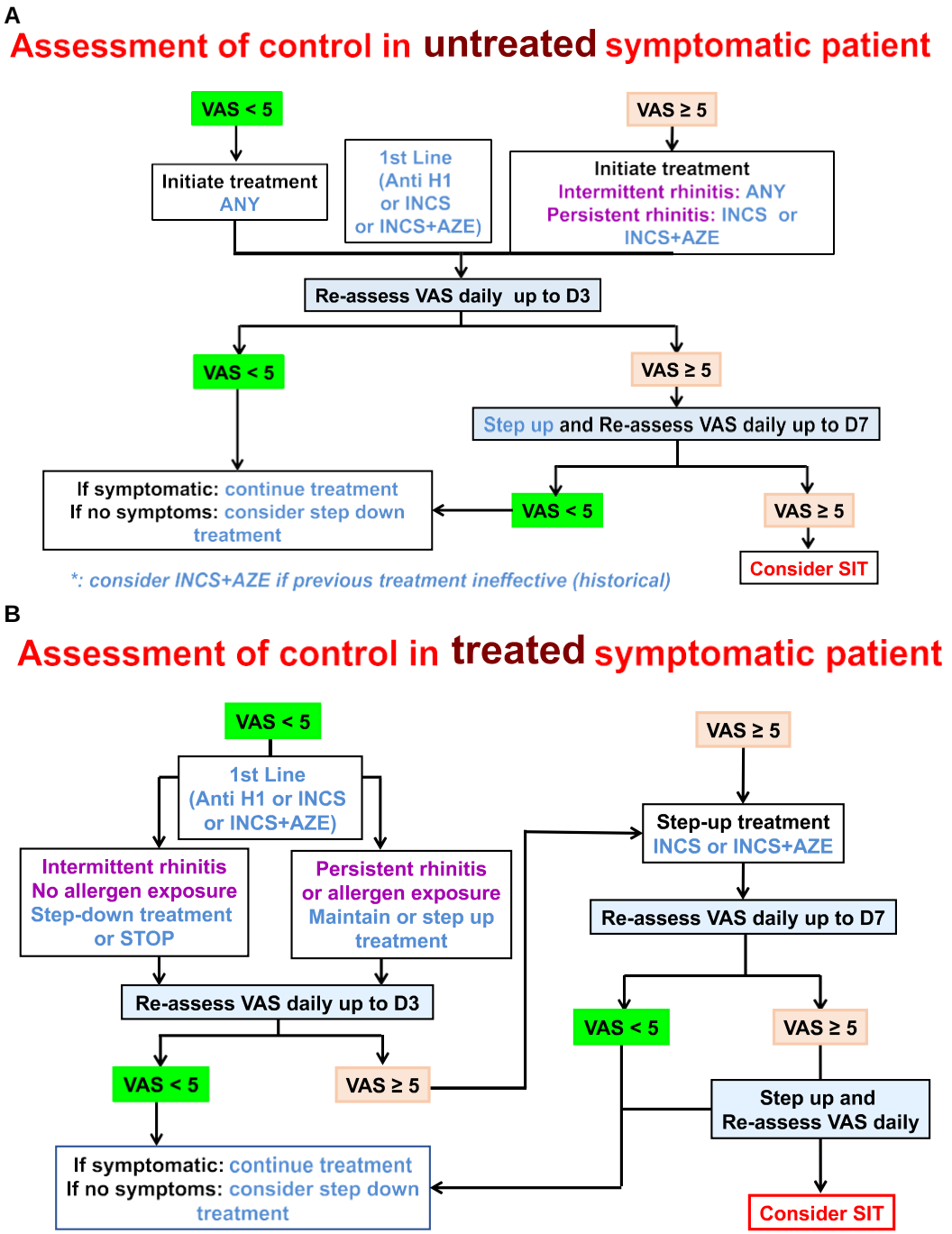

FIG 3. A, Step-up algorithm in untreated patients using VASs (adolescents and adults).[5] The proposed algorithm considers the treatment steps and the patient's preference. VAS levels are shown in ratios. If ocular symptoms remain once treatment has been initiated, add intraocular treatment. B, Step-up algorithm in treated patients using VASs (adolescents and adults).[5] The proposed algorithm considers the treatment steps and the patient's preference. VAS levels are shown in ratios. If remaining ocular symptoms, add intraocular treatment.

step up or step down treatment depending on control (Fig 3).[5] The ARIA algorithm for allergic rhinitis was revised by an expert group, and a proposal was made to classify allergic rhinitis treatments (Table I).[6]

ARIA 2010, 2016 revision, and US Practice Parameters 2017

Although few head-to-head comparisons of medications during randomized controlled trials are available,[29-32] the comparison of

TABLE I. Classification of treatments used in patients with allergic rhinitis[6]

T1	Nonsedating H_1-antihistamine (oral, intranasal, and ocular), leukotriene receptor antagonists, or cromones (intranasal and ocular)
T2	INCSs
T3	INCSs + intranasal azelastine
T4	Oral corticosteroid as a short course and an add-on treatment
T5	Consider referral to a specialist and allergen immunotherapy

allergic rhinitis medications has been proposed by several reviews[1] and guidelines.[5,20-22] A health technology assessment evaluation concluded that most allergic rhinitis medications had a similar effect.[33] However, this study used a method that did not enable differentiation between medications.

The ARIA revision 2016[21] and US Practice Parameters 2017[22] were developed independently and used the same methodological approach: GRADE.[10-12] Interestingly, the same questions were considered. Two major outcomes were considered in the treatment of moderate-to-severe rhinitis: efficacy and speed of action (Table II).[21,22]

Although the GRADE approach suggests the use of all relevant evidence, developers of recommendations have focused on randomized controlled trials.

ARIA 2016 revision[21] and US Practice Parameters 2017[22] mainly based on Randomized Control Trials support the MACVIA algorithm.[5]

Speed of onset of action of medications

The US Food and Drug Administration has proposed 3 study types to assess the onset of action of allergic rhinitis medications[25,34]: the standard phase III double-blind randomized controlled trial, park setting studies, and allergen exposure chamber studies.[35] Randomized controlled trials are informative but cannot provide sufficient precision to assess onset of efficacy because they cannot allow repeated timing over short periods of time (minutes). Allergen exposure chambers offer some advantages over randomized controlled trials in assessing the onset of action of medications that can be demonstrated in minutes.[35] The allergen exposure chamber allows consistent allergen exposure. However, it is a manipulated *in vivo* procedure, whereas the park study mirrors real-life exposure. Park studies have not captured both the early time and the allergen exposure chamber. It appears that a crossover trial would be difficult with a park study because of variations in allergen exposure between days. On the other hand, the allergen exposure chamber cannot replace real-world allergen exposure but can only complement it. Allergen exposure chamber studies appear more robust than park studies. To date, the allergen exposure chamber studiesthat have been conducted have been monocentric and have followed protocols unique to each center. Because there are technical differences in each allergen exposure chamber, it isnot easy to compare the results obtained in the different allergen exposure chambers,[36] although standardization has begun for some of them.[37]

In the Ontario and Vienna allergen exposure chambers, several medications have been tested (Table III).[26,27,38-51]

TABLE II. Overall recommendations using GRADE

ARIA 2016[21]

1. In patients with SAR, we suggest either a combination of INCS + OAH or INCS alone, but the potential net benefit might not justify spending additional resources.
2. In patients with PAR, INCSs alone are recommended rather than a combination of an INCS + an OAH.
3. In patients with SAR, we suggest either a combination of an INCS + an INAH or an INCS alone, but the choice of treatment de- pends on patient preferences. At initiation of treatment (first 2 weeks), a combination of an INCS + an INAH might act faster than an INCS alone and might therefore be preferred by some patients. In settings in which the additional cost of combination therapy is not large, a combination therapy might be a reasonable choice.
4. In patients with PAR, we suggest either a combination of an INCS + an INAH or an INCS alone.

For all of these recommendations, the level of evidence was low[2,3] or very low.[1,4]

US practice parameters 2017[22]

For initial treatment of nasal symptoms of SAR in patients ≥12 years of age, clinicians:

- should routinely prescribe monotherapy with an INCS rather than a combination of an INCS and an oral H_1-antihistamine or
- should recommend an INCS over an LTRA (for ≥15 years of age).
- For moderate-to-severe symptoms, clinicians can recommend the combination of an INCS and an INAH.

INAH, Intranasal antihistamine; *LTRA*, leukotriene receptor antagonist; *OAH*, oral antihistamine; *PAR*, perennial allergic rhinitis; *SAR*, seasonal allergic rhinitis.

The Ontario chamber studies show the rapid onset of efficacy for azelastine and its combinations. There does not seem to be a difference between azelastine alone or in combination. Other intranasal H_1-antihistamines have a slower onset of action. Intranasal corticosteroids (INCSs; alone or with oral H_1-antihistamines) are not effective before 2 hours. The Vienna chamber studies show that azelastine and levocabastine/fluticasone furoate are the fastest-acting medications by comparison with oral H_1-antihistamines.

RWE using mobile technology

According to the World Health Organization (WHO), Mobile Health (mHealth) has the potential to transform health service delivery globally.[52] Next-generation ARIA guidelines should consider testing recommendations based on the GRADE approach with direct RWE by using data obtained by using mHealth tools to confirm or refine current GRADE-based recommendations.

Although many mHealth tools are available for the assessment of allergic rhinitis,[53] only MASK has reported data on medications that can be used in RWE. MASK, a new development of ARIA, is an information and communication technology system centered around the patient (adolescents and adults).[19,54] MASK, which is freely available in the Google Play and Apple Stores, can inform patient decisions on the basis of a self-care plan proposed by the health care professional.[18,19] It uses a treatment scroll list including all medications customized for each country, as well as VASs to assess rhinitis control andwork productivity. MASK is deployed in 23 countries and 17 languages,[55] with more than 30,000 users. It was selected by the European Commission's Directorate-General for Health and Food Safety and by the newly established Commission Expert Group ''Steering Group on Health Promotion, Disease Prevention

TABLE III. Comparison of the time of onset of action using environmental exposure chambers

Drug (dose)	Formulation	Onset of action	Parameter	Reference
Ontario environmental exposure chamber[38]				
Azelastine	Nasal spray	15 min	TNSS	38
MPAzeFlu	Nasal spray	5 min	TNSS	37
Fluticasone propionate 1 oral loratadine (10 mg)	Nasal spray 1 tablet	160 min		
Olopatadine	Nasal spray	90 min	TNSS	39
Ciclesonide	Nasal spray	60 min	TNSS	40
Budesonide	Nasal spray	8 h	TNSS	41
Budesonide and azelastine	Nasal spray	20 min		
CDX-313 (solubilized budesonide 1 azelastine)	Nasal spray	20 min		
Levocetirizine	Tablet	160 min	MSS	42
Vienna environmental exposure chamber				
Astemisole-D, Loratadine-D	Tablet	65-70 min	No placebo MSS	43
Astemisole, loratadine, terfenadine-forte	Tablet	107-153 min	No placebo MSS	44
Azelastine (intranasal), desloratadine	Nasal/tablet	Azelastine: 15 min Desloratadine: 150 min	TNSS	45
Bilastine, cetirizine, fexofenadine	Tablet	No assessment before 60 min	TNSS	46
Cetirizine-D, budesonide	Nasal/tablet		No placebo	47
Cetirizine-D, xylometazoline nasal spray	Nasal/tablet		No placebo	48
Desloratadine	Tablet	30 min	Obstruction	49
Fluticasone furoate and levocabastine	Nasal spray	Combi: 15 min No data for fluticasone furoate or levocabastine	TNSS	50
Levocetirizine, loratadine	Tablet	Levocetirizine: 45 min Loratadine: 60 min	MSS	51
Rupatadine	Tablet	15 min	TNSS	52

Aze, Azelastine hydrochloride; *MSS*, mixed symptom score; *TNSS*, total nasal symptom score.

TABLE IV. Information used to support next-generation ARIA-GRADE guidelines

	GRADE recommendation	mHealth RWE	Chamber studies
Oral H_1-antihistamines are less potent than INCSs BUT many patients prefer oral drugs	21 No information on patient's preference	24,25 No information on patient's preference	
Intranasal H_1-antihistamines are less effective than INCSs	21		
Intranasal H_1-antihistamines are effective within minutes	21		40, 46
INCSs should continue being prescribed as first-line therapy in patients with moderate-to-severe rhinitis	21, 23	24, 25	
Onset of action of INCSs takes a few hours to a few days (ciclesonide has a faster onset)	21		42, 43
The combination of INCSs and oral H_1-antihistamines offers no advantage over INCSs	22, 23	24, 25	
The combination of INCSs and intranasal H_1-antihistamines is more effective than INCSs	YES in patients with moderate-to-severe disease: 23 With restriction: 22	24, 25	
The combination of INCSs and intranasal H_1-antihistamines is effective within minutes			39, 43, 51
Leukotriene antagonists are less potent than INCSs	23		39, 43, 51

The studies are summarized in the Online Repository.

and Management of Non-Communicable Diseases'' as a good practice that can be scaled up in the field of digitally enabled, integrated, person-centered care.[56]

Messages from MASK. Two studies in more than 9000 users and 22 countries[24,57] confirmed a pilot study[23] and allowed differentiation between allergic rhinitis treatments. They also showed that the assessment of days was useful in understanding treatment patterns. Their results combine to indicate that the following are true in real life:

1. Patients are poorly adherent to treatment.[23,57]
2. No treatment trajectory could be identified,[24] and most patients self-medicate.
3. Most patients with rhinitis use on-demand treatment when their symptoms are suboptimally controlled. When symptoms are uncontrolled, they change their medications daily for control.[23]
4. The vast majority of patients do not follow guidelines or physicians' prescriptions.[23,24,57]

TABLE V. Consensus opinion for the different scenarios[6]

	Patient VAS	Phenotype	Tx	Consensus
Part 1: Approach to treatment				
1	≥5	IAR or PER	Yes	Step-up
2	≥2 to <5	IAR	Yes	Continue
3	<2	IAR	Yes	Step-down
4	≥2 to <5	PER	Yes	Continue or step-up
5	<2	PER	Yes	Step-down
6	≥5	IAR	No	Initiate
7	≥5	PER	No	Initiate
8	<5	IAR or PER	No	Initiate

	Current Tx	Step-ups	Notes
Part 2: Specific treatment step-ups			
9	T1	T2 or T3	
10	T2	T3	
11	T3	T3 + T4*	Consider T5†
12	T1 + T2	T3	Consider T5†
13	T1 + T3	T3 + T4*	Consider T5†
14	T2 + T3	T3 + T4	Consider T5†
15	T5 + VAS ≥5	T5 + T>2 or T3	
16	T5 + VAS ≥2 to <5	T5 + T1, T2 or T3	T5 + T2 or T3 if congestion
17	T5 + T1	T5 + T2 or T3	
18	T5 + T2	T5 + T3	
19	T5 + T3	Continue	Consider referral

	Current Tx	Step-down	Notes
Part 3: Specific treatment step-downs			
20	T3	T2 or T1	T2 if congestion
21	T2	T1	Continue T2 if congestion
22	T1	Stop	Not exposed to allergen
23	T1	Continue	Exposed to allergen
24	T1 + T2	T1 or T2	T2 if congestion
25	T1 + T3	T1 or T3	T3 if congestion
26	T2 + T3	T2 or T3	
27	T5 + T3	T5 + T1 or T2	T5 + T2 if congestion
28	T5 + T2	T5 + T1	Continue T5 + T2 if congestion
29	T5 + T1	T5	Not exposed to allergen
30	T5 + T1	T5 + T1	Exposed to allergen
31	T5	T5	Until end of course

	Patients	Tx	Consensus	Note
Part 4: Treatment initiation				
32	IAR; VAS ≥5	No	T1, T2, or T3	T2 or T3 if congestion
33	PER; VAS ≥5	No	T2 or T3	
34	IAR or PER VAS <5	No	T1, T2, or T3	T2 or T3 if congestion

IAR, Intermittent allergic rhinitis; *PAR*, persistent allergic rhinitis; *T1*, antihistamine (oral, intranasal, or eyedrop), leukotriene receptor antagonist or cromones (intranasal or eyedrops); *T2*, INCS; *T4*, INCS + intranasal antihistamine; *T5*, consider referral and allergen immunotherapy; *Tx*, treatment.
*Short course (3-7 days).
†If VAS score remains ≥5/10.

5. When physicians are allergic, they behave like patients,[58] suggesting the need for behavioral science to improve control.
6. Patients who do not take medications usually have well-controlled symptoms.[23,24]
7. Patients reporting monotherapy with INCS-containing medications have a similar control level.[23,24] However, azelastine–fluticasone propionate combination (MPAze-Flu) is significantly more often administered as a single therapy than fluticasone furoate or mometasone furoate.
8. Patients reporting oral H_1-antihistamine monotherapy have a poorer level of control than those reporting INCS-containing medications.[23,24]
9. Most patients have a worse control level with increasing medications,[23,24] contradicting guidelines that propose to increase the treatment level to achieve control.
10. These results indicate that when patients' symptoms are controlled, either they do not take a medication or remain with a single treatment. When their symptoms are uncontrolled, they comedicate.

11. Considering control level and comedication, MPAzeFlu is more effective than INCSs.[23,24]
12. Resistant hypertension is defined by the number of medications used to control the disease,[59] and a similar classification might be proposed in patients with allergic rhinitis, confirming the severe chronic upper airway disease concept.[60]

Limitations of MASK. As for all studies using participatory data, potential biases include (1) the likelihood of sampling bias, which makes it difficult to assess the generalizability of the study; (2) outcome misclassification that cannot be assessed; and (3) because of ethical considerations, availability of very little information on patient (or day) characteristics. App users are not representative of all patients with rhinitis.

MASK studies have used days in cross-sectional analyses[18,19] because there is no clear pattern for a defined treatment, and a longitudinal study was not feasible because users mostly use the app intermittently.

The diagnosis of allergic rhinitis was not supported by a physician but was a response to the following question: ''Do you have allergic rhinitis? Yes/no.'' Therefore some users with no rhinitis might have responded ''yes'' to the question, but more than 95% of responders declared symptoms of rhinitis by questionnaire. There are potential measurement biases when using apps, including collection of information, education of the patient, age, availability, and ability to use a smartphone.[23] Precise patient characterization is impossible using an app, but every observational study using MASK has been able to identify days with poor control or criteria of severity.[61-65]

Adherence to treatment is impossible to obtain directly because patients do not report data every day and might not report all medications used. Electronic counters on delivery devices could be used to obtain more complete data on adherence.

Nonetheless, mobile technology is becoming an important tool for better understanding and managing allergic rhinitis. It adds novel information that was not available with other methods.[61-67] In addition, the mere number of observations that mobile technology can provide offers an unprecedented body of evidence that can complement conventional randomized controlled trials for RWE.

Other RWE studies using mobile technology. To our knowledge, no other mHealth study has assessed the efficacy of different medications on a large scale.

Physician's perspectives

There is a complete disconnection between the physician's prescriptions and the patient's behavior for the treatment of pollen-induced allergic rhinitis. The vast majority of allergists prescribe medications for the entire season, recommending the patient to use them regularly, even during days with few symptoms. Some allergists prescribe a preseason treatment without clear evidence of efficacy. On the other hand, the vast majority of patients use their medications on demand when their allergic rhinitis is not well controlled and they do not follow guidelines.[18,19]

When physicians are patients themselves, they behave like patients when they treat their own allergic rhinitis and do not follow the prescriptions, as recently reported.[58] Health literacy is an important component of adherence to medications,[68,69] but given the behavior of allergists as patients, it appears that other factors are more important. Possibly, it is human nature that drives adherence to treatment irrespective of whether the patient is a physician, and behavioral science is an important need to be considered in medical care.

Lack of adherence is very common in allergists with allergic rhinitis and prescribed long-term treatment.

NEXT-GENERATION ARIA-GRADE GUIDELINES

Recommendations have been refined with RWE and chamber studies (Table IV).[20-24,38,39,41,42,45,50] The algorithm proposed in Fig 3 is also supported by the present data.

The approach proposed in this article confirms most GRADE recommendations for allergic rhinitis and the classification of allergic rhinitis treatments proposed by ARIA (Table I).[6] Some conditional evidence was supported by RWE:

- The combination of oral H_1-antihistamines with INCSs was not found to be more effective than INCSs alone.
- The combination of intranasal H_1-antihistamines with INCSs was found to be more effective than INCSs alone.
- Intranasal H_1-antihistamine–containing medications are effective within minutes.

NEXT-GENERATION ARIA ALGORITHM

The overall ARIA algorithm[5] was found to be appropriate, and no change is needed. The step-up and step-down approach proposed by ARIA experts[6] based on the ARIA algorithm has been confirmed (Table V). However, the different steps need further validation with RWE.

CONCLUSIONS

In this report we present the first GRADE-based guideline integrating RWE and supportive studies (chamber studies) in the management of allergic rhinitis. This approach could be considered a model for chronic diseases.

These guidelines will inform ICPs and will be included in the European Commission's Directorate-General for Health and Food Safety digitally-enabled, integrated, person-centered care.[70] They will represent the change management strategy of ARIA, phase 4.[16]

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SUPPLEMENTARY DATA

Although many mHealth tools are available for the assessment of AR,[E1] only MASK has reported data on medications that can be used in RWE. MASK, a new development of ARIA, is an information and communication technology system centered around the patient in adolescents and adults.[E2,E3] MASK, which is freely available in the Google Play and Apple stores, can inform patient decisions on the basis of a self-care plan proposed by the health care professional.[E2,E4-E11] It uses a treatment scroll list including all medications customized for each country and a VAS to assess rhinitis control and work productivity. MASK is deployed in 23 countries and 17 languages,[E12] with more than 26,000 users. It was selected bythe European Commission's Directorate-General for Health and Food Safety and the newly established Commission Expert Group ''Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases'' as a good practice in the field of digitally enabled, integrated,person-centered care.[E13]

2016 MASK treatment study[E7]

Background. A pilot study attempted to provide additional and complementary insights into real-life treatment of allergic rhinitis using MASK.

Methods. MASK collected daily VAS scores for overall allergic symptoms (VAS global) in 15 countries. Because of privacy concerns, MASK, as any other mobile technology, cannot assess the characteristics of the patient.

Results. Two thousand eight hundred seventy-one users filled in 17,091 days of VASs between June 1, 2015, and May 30, 2016. Medications were reported for 9,634 days.

- Patients did not follow guidelines and often self-medicated.
- Adherence to treatment was poor.
- MASK allowed differentiation between treatments within or between classes (INCS containing medications and oral H_1-antihistamines). Untreated days (days reported without any treatment) had the best control. Days with reported INCSs or MPAzeFlu had similar control. Days with cetirizine alone had worse control. Days with loratadine alone or any cotherapy had the worst control.
- Users reporting intranasal MPAzeFlu used comedication on 30% to 35% of days, whereas those reporting INCSs used comedication on 45% to 60% of days.
- Very few users reported oral corticosteroids, and VAS levels were usually high.
- This RWE study brings new information on the treatment of patients with AR, suggesting the following: First, patients treat themselves as needed depending on disease control and increase their treatment when they are unwell. However, comedication does not improve the median control. Second, MPAzeFlu is superior to INCSs because, when symptoms are controlled, patients do not comedicate,and comedication is more common in those who used INCSs.

The MASK 2016 study indicated low adherence and allowed comparative efficacy of medications by using a novel approach.

2017 MASK treatment study[E14]

Objectives. A cross-sectional real-world observational study was undertaken in 22 countries to complement the 2017 pilot study.[E7]

Methods. MASK was used to collect data of daily VAS scores for (1) overall allergic symptoms; (2) nasal, ocular, and asthma symptoms; and (3) work, as well as medication use. The 3 most common intranasal medications containing INCSs (fluticasone furoate, mometasone furoate, and fluticasone propionate), MPAzeFlu, and 8 oral H_1-antihistamines were studied. The study included some of the users of the pilot study (to achieve a sufficient number of users per drug), [E7] but outcomes differed.

Results. Nine thousand one hundred twenty-two users filled in 112,054 days of VASs in 2016 and 2017 (Fig E1).

- As shown in the pilot study,[E7] similar control levels were found for single treatment with INCSs or MPAzeFlu (good control), but more users needed INCSs to be combined with another treatment (worst control) compared with MPAzeFlu.
- INCSs or MPAzeFlu resulted in more control days than oral H_1-antihistamines.
- The same trend was found for VAS scores for asthma, eye symptoms, and work productivity.

The 2017 MASK treatment study confirms MASK's usefulness in assessing behavior in patients with allergic rhinitis. A ranking of medications was possible and confirmed the MASK 2016 study. The 2 MASK treatment studies indicated that MPAzeFlu is the most effective and oral H_1-antihistamines are the least effective category of medication.

2018 MASK adherence study[E15]

Background. Mobile technology might help better understand adherence to treatment.

Objectives. We sought to assess adherence to treatment in patients with allergic rhinitis using the MASK app.

Methods. An observational cross-sectional study was carried out on all consecutive users who filled in MASK from January 1, 2016, to August 1, 2017. Secondary adherence was assessed by using modified medication possession ratio (MPR) and proportion of days covered (PDC is a newer and more conservative measure of refill record–based adherence).

- Proportion of MPR (modified MPR): ratio of days of medication use was reported to be used on days in a given time interval.
- PDC over a time interval (modified PDC): ratio of days of medication was reported to be used on days in the time interval between the first and the last record considered.

Results. Twelve thousand one hundred forty-three users were registered, and 6949 users had at least 1 VAS recording. Among them, 1887 (15.7%) users had 7 or more days of reporting VAS scores. One hundred thirty-six (11.28%) of them were adherent (MPR $\geq$ 70% and PDC $\leq$ 1.25).

The 2018 MASK adherence study indicated that adherence to treatment was estimated to be less than 5%.

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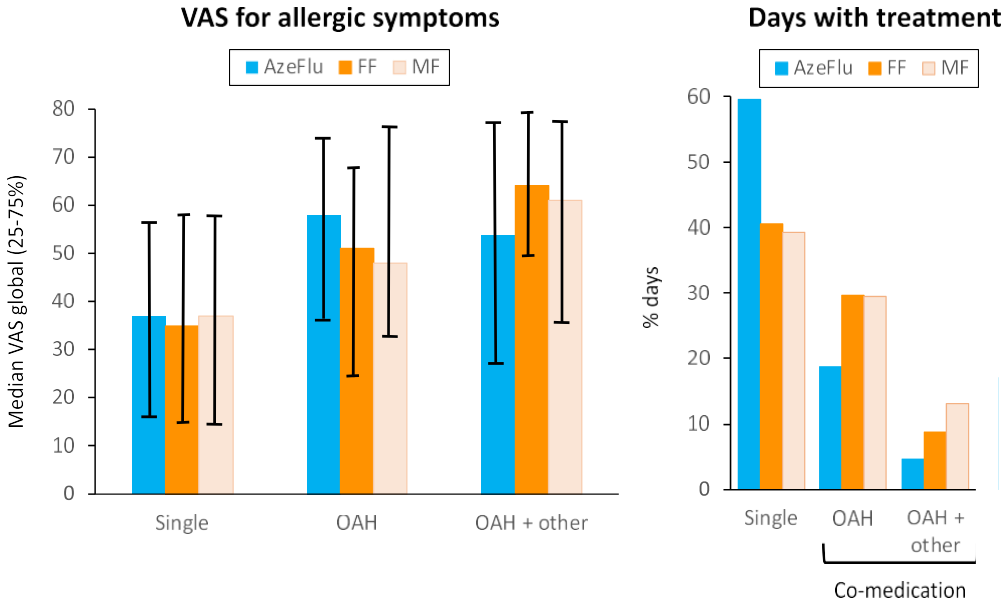

FIG E1. Efficacy of INCS-containing medications (VAS global) and percentage of days with comedications. *FF*, Fluticasone furoate; *MF*, mometasone furoate; *OAH*, oral H_1-antihistamine; *Other*, any other medication; *Single*, no comedication.

Summary of childhood asthma guidelines, 2021: A consensus document

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Asthma is the most common chronic illness of childhood. The prevalence is rising and the mortality and morbidity from asthma are unacceptably high in South Africa. It is important to make a correct diagnosis based, most importantly, on the clinical history and supported by investigations. The appropriate drug and device must be chosen to achieve good asthma control. Patients must be followed up regularly and their asthma control must be assessed. The treatment can then be adjusted according to the level of control. The COVID-19 pandemic has placed new challenges on the care of our asthmatics. Asthma education and adherence are important components of management of the condition.

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The South African Childhood Asthma Working Group (SACAWG), a sub-committee of the Allergy Society of South Africa (ALLSA), first published its guidelines for the management of chronic asthma in children and adolescents in 1992, followed by revisions in 1994, 2000 and 2009.[1-8] In the interim, there have been a number of key changes in the diagnostic criteria (particularly in young children, assessment of asthma control, management principles, new drugs, new drug-delivery devices and assessment of asthma control and risk). This new updated consensus statement attempts to provide an update on the management of childhood asthma, incorporating new information and including a section on COVID-19. The full document appears on the ALLSA website (https://allsa.org).

Asthma prevalence

Asthma is the most common chronic respiratory disorder in childhood. The prevalence of asthma in childhood is high and is rising. Asthma is underdiagnosed and undertreated.

Asthma diagnosis

Asthma should be diagnosed in children who present with episodes of variable expiratory airflow limitation. It remains a largely clinical diagnosis, which should be supported by lung function testing in school-aged children. The symptoms may include episodic wheeze (due to bronchoconstriction), shortness of breath, difficult or laboured breathing, chest tightness and reduced activity withor without cough. The intensity varies over time and symptoms improve after correct use of a rapid-acting inhaled bronchodilator. The symptoms are not specific to asthma, and other conditions may mimic the condition. Chronic airway inflammation and variable expiratory airflow limitation define asthma. We propose the followingfour steps to guide the clinician.

Children <6 years of age

Step 1. History taking

This is the most important step. The inception of asthma is associated with a number of risk factors (refer to the main document on the ALLSA website: https://allsa.org).

The history regarding the features of episodes of wheezing assists in the diagnosis:

- **Variable airflow limitation.** A history of (preferably doctor-confirmed) bronchodilator-initiated improvement of wheeze will support an asthma diagnosis.
- **Severity of wheeze events.** A history of more severe wheeze (e.g. with respiratory distress or a need for oxygen supplementation) favours an asthma diagnosis, but does not exclude alternative diagnoses.
- **Frequency and duration of episodes.** Events that occur more frequently (>3 episodes per year) and that last longer (>10 days at

a time) may indicate an asthma diagnosis, but will not exclude an alternative reason.

- **Temporal pattern of symptoms.** Wheeze that does not only occur during airway infections, but also in response to other triggers in-between infections, supports an asthma diagnosis. Events that persist after 3 years of age, night-time worsening, an association with exercise or environmental change (e.g. cold air exposure) further support an asthma diagnosis.

Step 2. Exclude an alternative reason for wheezing episodes

The aim of the clinical examination is not only to find signs of asthma and other features of atopic disease (atopic dermatitis, allergicrhinitis, etc.) that may support an asthma diagnosis, but also tolook for clinical findings that would indicate an alternative reasonto wheeze (such as digital clubbing, growth faltering, asymmetric wheeze) (Table 1).

Step 3. Assess inflammation

Clinical features of other atopic disease (such as atopic dermatitis and allergic rhinitis) and the presence of allergen-specific IgE (through skin-prick testing or ImmunoCAP (ThermoFisher Scientific, USA)) may support an asthma diagnosis. A pragmatic therapeutic trial will confirm the presence of corticosteroid-responsive inflammation (Table 2).

A step-wise trial of correctly administered low-dose inhaled corticosteroid (ICS) should be followed when starting treatment in any child with a wheezing disorder. Treatment should be viewed as a *therapeutic trial* and the initial treatment response must be evaluated in 6 - 8 weeks.[9-12] If there is no clinical response to correctly administered ICS therapy, it should be discontinued, and the child investigated further. Symptoms that resolve during ICS therapy may be due to the natural history of a preschool wheezing disorder or to an effect of treatment. This must be distinguished by again withdrawing treatment. Treatment should only be restarted if symptoms recur. An ongoing benefit of ICS treatment should be reviewed every 3 months and the ICS kept at the lowest possible dose for symptom control.[10-15]

Step 4. Seek objective evidence of variable expiratory airflow limitation

A clinical assessment of the response to a correctly administered rapid-acting inhaled bronchodilator can be helpful. The clinician should pursue every opportunity to document improvement in wheeze and hyperinflation after the administration of a rapid-acting inhaled bronchodilator. The more it is confirmed clinically, the more likely that the correct diagnosis is asthma (Table 3).

Children 6 - 11 years of age

For children 6 - 11 years of age, the same steps as for younger children should be followed (Table 4). A proper history, exclusion of an alternative reason to wheeze and an assessment for inflammation should be undertaken. Objective evidence of variable expiratory airflow limitation can then be demonstrated and should ideally be

Table 1. Differential diagnosis of asthma in children <6 years of age

Infective	Structural	Functional
Bronchiolitis	Trachea and bronchomalacia	Wheezy phenotypes
Atypical infection	Tracheal webs	Primary ciliary dyskinesia
	Tracheal and bronchial stenosis	
Bacterial airway infection	Lymphadenopathy	Cystic fibrosis
	Tumours	
Laryngotracheobronchitis	Vascular compression	Gastro-oesophageal reflux disease
	Double aortic arch	
	Innominate artery compression	
	Left pulmonary artery sling	
	Patent ductus arteriosus ligament	
	Cardiac chamber or pulmonary artery enlargement	
Protracted bacterial bronchitis	Cystic lesions and masses	Retained foreign body
	H-type tracheo-oesophageal fistula	Pulmonary oedema/cardiac disease
	Laryngeal clefts	Interstitial lung disease
		Bronchiolitis obliterans
		Bronchopulmonary dysplasia
		Bronchiectasis
		Immunodeficiency
		Perceived tight chest

Table 2. Management of persistent asthma in children ≤6 years of age[9,17]

Intermittent asthma	Management of persistent asthma			
Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
SABA* and short course (7 - 10 days) of ICS at start of URTI	Daily low-dose ICS and SABA*	Medium-dose ICS, or, in children >4 years of age, daily low-dose ICS/LABA and SABA*	Daily medium-dose ICS/LABA and SABA* or medium-dose ICS plus LTRA	Refer to specialist

SABA = short-acting beta-2 agonist; ICS = inhaled corticosteroid; URTI = upper-respiratory tract infection; LABA = long-acting beta-agonist; LTRA = leukotriene-receptor antagonist.
*As needed.

done before commencement of controller therapy. Peak expiratory flow (PEF) measurements or, preferably, spirometry can be used (Table 3).[15] Normal test results do not exclude the diagnosis of asthma.[14] Where the history is suggestive of asthma, and the spirometry does not support the diagnosis, other specialised tests, such as exercise bronchoprovocation or methacholine challenge, may be done by a pulmonologist to confirm the diagnosis.

Goals of asthma treatment

The long-term goals of asthma management include the following:

- to achieve good symptom control
- to maintain normal activity levels
- to minimise future risk of asthma-related mortality
- to reduce exacerbations
- to maintain lung function and normal lung development
- to minimise side-effects of treatment
- to provide a written action plan
- to consider the patient's own goals with regard to treatment.

The goals of asthma management can only be achieved through an appropriate understanding between the patient, parent/caregiver and medical team. A cycle of *assess* (diagnosis, symptom control, risk factor assessment, medication technique and adherence), *adjust treatment* (medications, non-pharmacological strategies, treatment of modifiable risk factors) and *review response* (medication effects and side-effects), in combination with education of both the parent/caregiver and the child with regard to effective inhaler use, adherence, symptom monitoring and a written personalised action plan, should be done during every visit.

Asthma management

This involves avoidance of triggers, and pharmacological treatment.

Avoidance of triggers

Asthma triggers, such as exercise, are difficult to avoid. However, all attempts should be made to reduce exposure to avoidable triggers, particularly where a clear association between exposure andsymptoms is seen:

- environmental tobacco smoke and other indoor air pollutants
- control of indoor allergens, such as house-dust mites, pets, cockroach and mould allergy.

Treatment

Principles of asthma treatment

- Decide on the level of severity (Table 5).
- Choose the treatment, based on severity (Tables 6 - 8).

Table 3. Confirmation of variable airflow limitation with peak expiratory flow or spirometry[15]

Confirmation of variable expiratory airflow limitation
For PEF measurements
PEF variability with an average daily diurnal variability >13% when documented twice daily for 2 weeks
Positive exercise challenge test with decrease in PEF >15% after reaching target heart rate (0.8 × 220 minus age in years)
Excessive variation of PEF >15% between outpatient visits (using the same equipment) with or without airway infections
For spirometry measurements
Decreased FEV_1/FVC ratio due to decreased FEV_1 (normal ratio >0.9)
Positive bronchodilator reversibility with increase in FEV_1 >12%
Positive exercise challenge test with decrease in FEV_1 >12% after reaching target heart rate (0.8 × 220 minus age in years)
Excessive variation of FEV_1 >12% between outpatient visits (using the same equipment) with or without airway infections

PEF = peak expiratory flow; FEV_1 = forced expiratory volume; FVC = forced vital capacity.

Table 4. Management of persistent asthma in children 6 - 11 years of age[9,17]

Intermittent asthma	Management of persistent asthma			
Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
SABA* and short course (7 - 10 days) of ICS at start of URTI or daily low-dose ICS	Daily low-dose ICS and SABA* or LTRA or low-dose ICS when SABA is taken	Daily and as-needed low-dose ICS/ LABA (formoterol) combination or low-dose ICS/ LTRA	Daily and as-needed medium-dose ICS/LABA (formoterol) combination or high-dose ICS/LABA or add LTRA or add tiotropium	Refer for expert advice for assessment for anti-IgE therapy or other biologic therapy or daily and as-needed high-dose ICS/LABA combination plus LRTA

SABA = short-acting beta-2 agonist; ICS = inhaled corticosteroid; URTI = upper-respiratory tract infection; LTRA = leukotriene-receptor antagonist; LABA = long-acting beta-agonist.
*As needed.

Table 5. Classification of asthma severity based on symptoms and lung function presenting for the first time without treatment[16]

	Mild intermittent (step 1)	Mild persistent (step 2)	Moderate persistent (step 3)	Severe persistent (step 4)
Symptoms	≤2/week	>2/week	Daily symptoms	Continual symptoms
Night-time symptoms	≤2/month	>2/month	>1/week	Frequent
PEF (predicted), %	≥80 predicted	≥80 predicted	>60 - ≤80	≤60
PEFR variability, %	<20	20 - 30	>30	>30

PEF = peak expiratory flow; PEFR = peak expiratory flow rate.

Table 6. Preferred low-dose inhaled corticosteroid in children <5 years of age

Inhaled corticosteroid	Total daily inhaled dose, µg
Beclomethasone dipropionate (HFA)	100
Budesonide (pMDI and spacer)	200
Budesonide (nebulised)	500
Fluticasone propionate (HFA)	100

HFA = hydrofluoroalkane; pMDI = pressurised metered-dose inhaler.

- Choose an appropriate device and delivery system.
- Start treatment.
- Review in 4 - 6 weeks.
- Assess asthma control (Table 9).
- Step up or step down treatment, depending on level of control.

Metered-dose inhalers

The most common asthma pump is the metered-dose inhaler (MDI), preferably with a spacer. Spacers comprise a simple holding chamber with or without a valve. The medication is suspended within the

Table 7. Estimated equipotent daily dosage of inhaled corticosteroid for children 6 - 11 years of age

Drug	Low daily dose, µg	Medium daily dose, µg	High daily dose, µg
Children 6 - 11 years of age			
Beclomethasone dipropionate	100 - 200	200 - 400	>400
Budesonide*	100 - 200	200 - 400	>400
Ciclesonide*†	80	80 - 160	>160
Fluticasone propionate‡	100 - 200	200 - 500	>500
Mometasone furoate	110 - 220	220 - 440	>440
Triamcinolone acetonide	400 - 800	800 - 1 200	>1 200
Adolescents ≥12 years of age			
Beclomethasone dipropionate HFA§	100 - 200	>200 - 400	>400
Budesonide*	200 - 400	>400 - 800	>800
Ciclesonide	80 - 160	>160 - 320	>320
Fluticasone propionate‡	100 - 250	>250 - 500	>500
Mometasone furoate	110 - 220	>220 - 440	>440

HFA = hydrofluoroalkane; CFC = chlorofluorocarbon.
*Approved for once daily dosing in patients with mild illness.
†Ciclesonide is registered for children ≥12 years of age.
‡May be used at half the dose of budesonide equivalent.
§As CFC preparations are taken off the market, medication inserts for HFA preparations should be carefully reviewed for the equivalent correct dosage.

Table 8. Combination products available in South Africa

Combination	Device	Dose, µg
Fluticasone proprionate/salmeterol	DPI (Accuhaler)	100/50
		250/50
		500/50
Fluticasone proprionate/salmeterol	pMDI	50/25
		125/25
		250/25
Budesonide/formoterol fumarate	pMDI	80/4.5
		160/4.5
Budesonide/formoterol fumarate	DPI (Turbuhaler)	80/4.5
		160/4.5
		320/9
Fluticasone furoate/vilanterol	pMDI	100/25
Mometasone furoate/formoterol fumarate	pMDI	100/5
Mometasone furoate/formoterol fumarate	pMDI CFC free	100/5
		200/5

pMDI = pressurised metered-dose inhaler; DPI = dry-powder inhaler; CFC = chlorofluorocarbon.

Table 9. GINA assessment of asthma control and future risk in children <5 years of age, 6 - 11 years of age, adolescents and adults

Symptom control	Well controlled	Partly controlled	Uncontrolled
In the past week, has the patient had:	None of these	1 - 2 of these	3 - 4 of these
• Daytime asthma symptoms more than twice per week?			
• Night-time awakening due to asthma?			
• Reliever (SABA) use more than twice per week?			
• Limitation of activity?			

GINA = Global Initiative for Asthma; SABA = short-acting beta-2 agonist.

spacer and then breathed in, enhancing lung deposition. A spacer is recommended for all children and adults with difficult-to-control asthma. A very effective spacer device can be constructed out of a 500 mL plastic cold-drink bottle. A hole large enough to take the mouthpiece of an MDI is cut (or burnt) in the bottom end of the bottle to form a simple low-cost non-valved spacer.

Nebulisers

Home nebulisers are not recommended for asthma management.

Dry-powder inhalers

Dry-powder inhalers (DPIs) are easy to use, but are only suitable for older children and adults because of the inspiratory flow required for their actuation. Measurements of peak inspiratory flow can be done with appropriate devices to assess suitability of DPIs.

Asthma control

Asthma control is the extent to which the effects of asthma can be seen in a patient or have been reduced or removed by treatment.[9] Evaluation of asthma control includes two broad concepts, i.e. *symptom control* and *future risk* of adverse outcomes. Symptom control is assessed by frequency of symptoms, reliever medication use and activity limitation over the past week and month.

Future risk refers to the possibility of exacerbations, medication side-effects (oral symptoms and impaired growth in children) or loss of lung function. No test is a gold standard and all tests must be used in conjunction with a good history and clinical examination to assess control.[18,19] After initiation of treatment, it is essential to assess asthma control at every follow-up visit, no less than 6-monthly, and to adjust treatment accordingly.

Advice for asthmatics to avoid viral-induced exacerbations

The common steps individuals take to avoid influenza and other respiratory infections also protect from the coronavirus:

- Keep a distance from others (social distancing, ~1 m).
- Avoid people who are sick.
- Avoid crowded venues.
- Wash your hands often for 20 - 30 seconds, always after coughing or sneezing.
- Disinfect surfaces, but avoid disinfectants that precipitate asthma exacerbations.

Wearing a mask to protect people from coronavirus in public spaces is now recommended by the World Health Organization(WHO), and is also endorsed for patients with asthma. There isno evidence to suggest that mask-wearing is deleterious to people with asthma.

Asthma education

Asthma education is an important part of the management of asthmatics. Patients must be informed of triggers and the need for adherence, and should be given a written treatment action plan.

Treatment adherence

Adherence to asthma treatment in the paediatric population is poor, with studies reporting only one-third of children using ICS therapy appropriately. Assessing adherence is part of the clinical assessment of the asthmatic child. Barriers to adherence may be intentional (driven by illness perceptions or medication beliefs, leading to patients and caregivers deliberately choosing not to follow treatment recommendations) or unintentional (related to family routines and socioeconomic factors).

Comorbidities

Identification and treatment of associated comorbidities may improve asthma control. These are:

- rhinitis or sinusitis
- obesity
- gastro-oesophageal reflux disease (GORD)
- Allergic bronchopulmonary aspergillosis (ABPA).

Summary of the changes

- In children <6 years of age with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections, we recommend starting a short course (7 - 10 days) of daily ICS atthe onset of a respiratory tract infection with an as-needed short- acting beta-2 agonist (SABA) for quick-relief therapy compared with as-needed SABA for quick-relief therapy only.
- In children 6 - 11 years of age we recommend as-needed SABA and a short course (7 - 10 days) of ICS at the start of an upper-respiratory tract infection or daily low-dose ICS.
- In children aged ≥6 years with moderate to severe persistent asthma, we recommend ICS-formoterol in a single inhaler as daily controller and reliever therapy compared with either higher-dose ICS as daily controller therapy and SABA for quick-relief or same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy.

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What's new in GINA 2023?

Global Strategy for Asthma Management and Prevention

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The Global Initiative for Asthma (GINA)

- GINA was established by the WHO and NHLBI in 1993
  - To increase awareness about asthma
  - To improve asthma prevention and management through a coordinated worldwide effort
  - Independent since 2014, funded only by the sale and licensing of its reports and figures
- The GINA Strategy Report is a global evidence-based strategy that can be adapted for local health systems and medicine availability; it is widely used (downloaded from >200 countries)
- The GINA Strategy Report is updated every year
  - Twice-yearly cumulative review of new evidence (including GRADE reviews)
  - Evidence integrated across whole asthma strategy, not isolated PICOT questions
  - Careful attention to study design, populations, and clinical relevance
  - Extensive external review
  - Practical focus: not just ‘what’, but ‘how’
- All members of GINA Science Committee are active in clinical asthma research
  - See www.ginasthma.com/about-us/methodology for handling of conflict of interest

Goals of asthma treatment

- Few asthma symptoms
- No sleep disturbance
- No exercise limitation

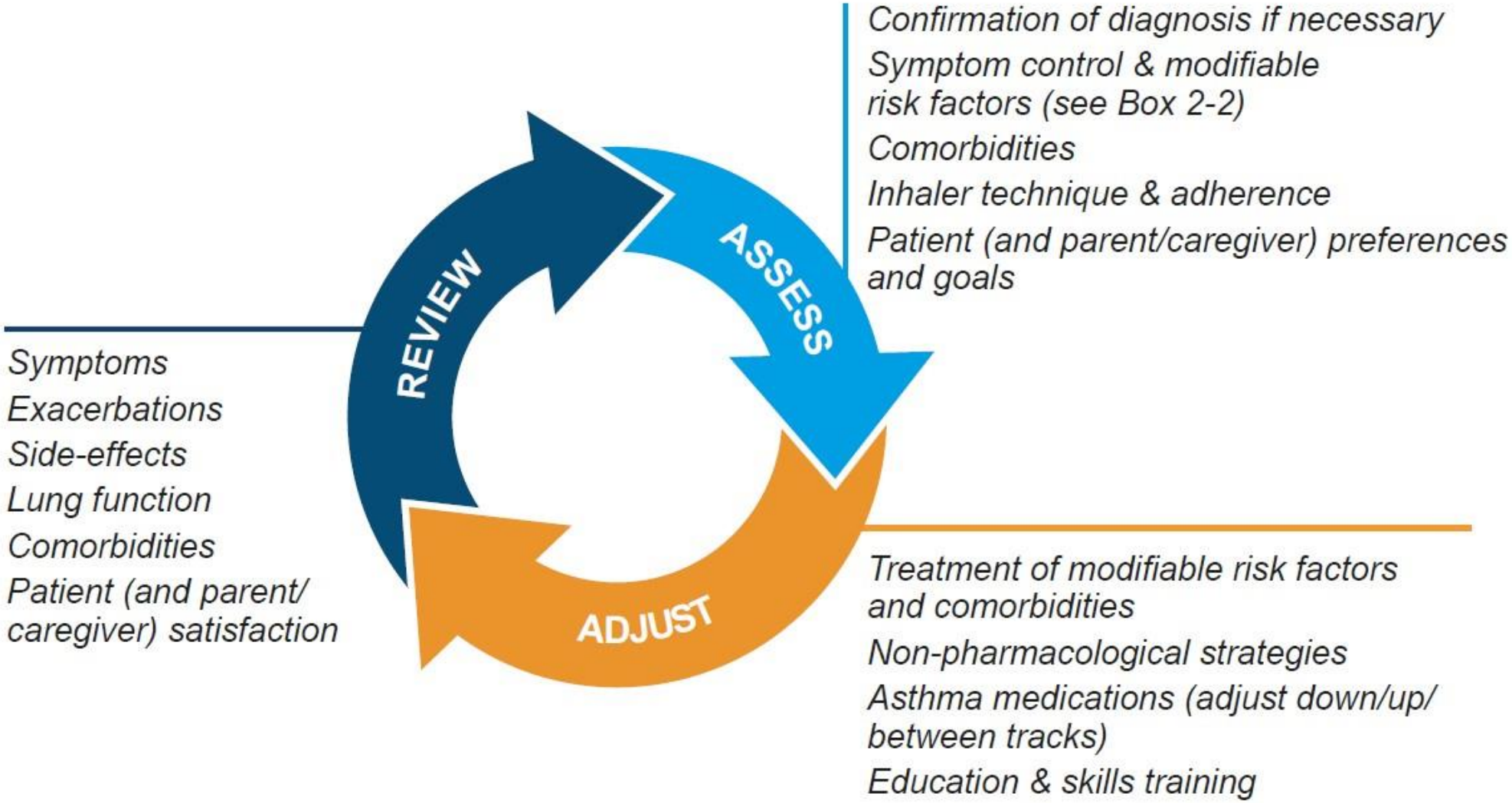
Symptom control (e.g. ACT, ACQ)

- Maintain normal lung function
- Prevent flare-ups (exacerbations)
- Prevent asthma deaths
- Minimize medication side-effects (including OCS)

Risk reduction

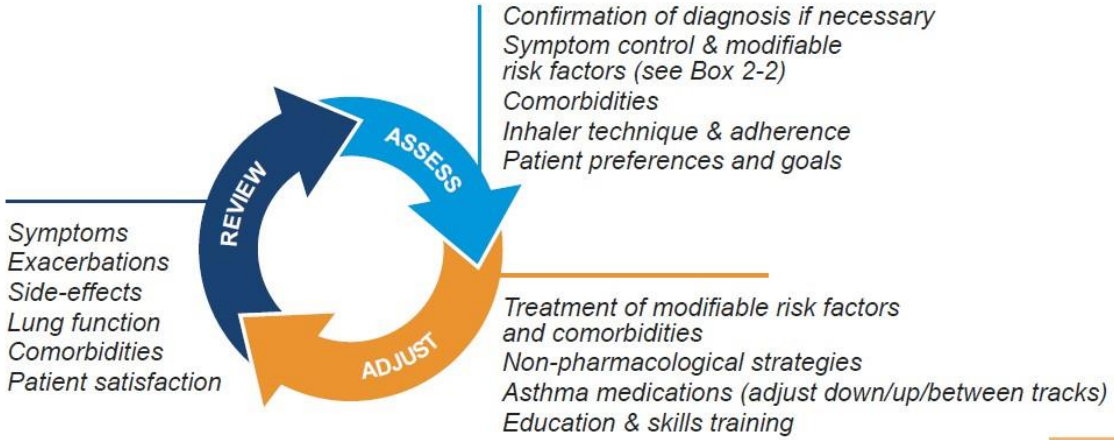
- The patient's goals may be different
- Symptom control and risk may be discordant
  - Patients with few symptoms can still have severe exacerbations

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; OCS: oral corticosteroids



GINA 2023 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol*			

See GINA severe asthma guide

TRACK 2: Alternative **CONTROLLER and RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: as-needed ICS-SABA*, or as-needed SABA				

Other controller options (limited indications, or less evidence for efficacy or safety – see text)	*Low dose ICS whenever SABA taken*, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory reliever (AIR)

GINA 2023 – Adults and adolescents
Track 1

Maintenance and reliever therapy (MART) with ICS-formoterol

As-needed-only ICS-formoterol ('AIR-only')

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2
As-needed-only low dose ICS-formoterol*

STEP 3
Low dose maintenance ICS-formoterol*

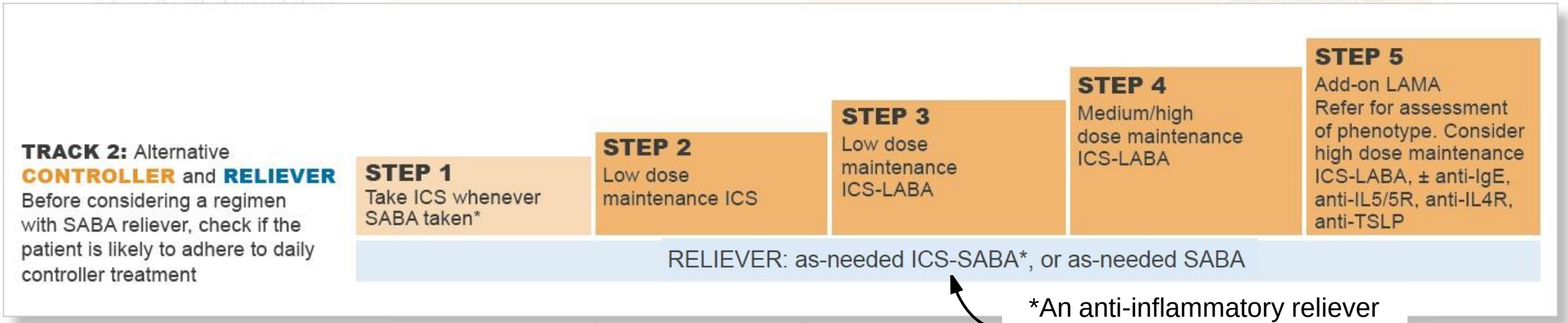
STEP 4
Medium dose maintenance ICS-formoterol

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

*An anti-inflammatory reliever (AIR)

GINA 2023 – Adults and adolescents
Track 2



*An anti-inflammatory reliever (Steps 3–5)

GINA 2023 – Adults and adolescents

Other controller options (limited indications, or less evidence for efficacy or safety – see text)		*Low dose ICS whenever SABA taken*, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

Terminology

- Reliever
  - For symptom relief, or before exercise or allergen exposure
- Controller
  - Function: targets both domains of asthma control (symptom control and future risk)
  - Mostly used for ICS-containing treatment
- Maintenance treatment
  - Frequency: regularly scheduled, e.g. twice daily

ICS: inhaled corticosteroid; SABA: short-acting beta$_2$-agonist

Terminology

- **A**nti-**I**nflammatory **R**eliever = **AIR**
  - e.g. ICS-formoterol, ICS-SABA
  - Provides rapid symptom relief, plus a small dose of ICS
  - Reduces the risk of exacerbations, compared with using a SABA reliever

Regimens with ICS-formoterol anti-inflammatory reliever

- As-needed-only ICS-formoterol = **AIR-only**
  - The patient takes low-dose ICS-formoterol whenever needed for symptom relief
- **M**aintenance **A**nd **R**eliever **T**herapy with ICS-formoterol = **MART**
  - A low dose of ICS-formoterol is used as the patient's maintenance treatment, plus whenever needed for symptom relief
- ICS-formoterol can also be used before exercise or allergen exposure

ICS: inhaled corticosteroid: SABA: short-acting beta$_2$-agonist; MART is sometimes also called SMART

Evidence: Steps 1–2

Track 1, Steps 1–2: As-needed-only low-dose ICS-formoterol

COMPARED WITH AS-NEEDED SABA

- Two studies *(SYGMA 1, O'Byrne et al, NEJM 2018, n=3836; Novel START, Beasley et al, NEJM 2019, n=668)*
- Risk of severe exacerbations was reduced by 60–64% *(SYGMA 1, Novel START)*

COMPARED WITH MAINTENANCE LOW DOSE ICS plus as-needed SABA

- Four studies *(SYGMA 1; SYGMA 2, Bateman et al, NEJM 2018, n=4176; Novel START; PRACTICAL, Hardy et al, Lancet 2019, n=885)*
- Risk of severe exacerbations similar *(SYGMA 1 & 2)*, or lower *(Novel START, PRACTICAL)*
- Symptoms very slightly more, e.g. ACQ-5 0.15 (vs 0.5 MCID), not worsening over 12 months
- Pre-BD FEV_1 slightly lower (~54 mL), not worsening over 12 months
- FeNO slightly higher (10ppb), not increasing over 12 months *(Novel START, PRACTICAL)*
- As-needed ICS-formoterol used on ~ 30% of days → average ICS dose ~50–100mcg budesonide/day
- Benefit independent of T2 status, lung function, exacerbation history *(Novel START, PRACTICAL)*
- Qualitative research: most patients preferred as-needed ICS-formoterol *(Baggott Thorax 2020, ERJ 2020; Foster Respir Med 2020, BMJ Open 2022)*

*Budesonide-formoterol 200/6 [160/4.5] mcg by Turbuhaler, 1 inhalation as needed for symptom relief

Track 1, Steps 1–2: As-needed-only low-dose ICS-formoterol

- Risk of severe exacerbations *(Crossingham et al, Cochrane 2021)*
  - Compared with as-needed SABA alone: **55% reduction** (OR 0.45 [0.34–0.60])
  - Compared with daily ICS plus as-needed SABA: (OR 0.79 [0.59–1.07])
- Risk of emergency department visits or hospitalizations *(Crossingham et al, Cochrane 2021)*
  - Compared with as-needed SABA alone: **65% reduction** (OR 0.35 [0.20–0.60])
  - Compared with daily ICS plus as-needed SABA: **37% reduction** (OR 0.63 [0.44–0.91])
  - Large population-level reduction in healthcare utilization

Track 2, Steps 1–2: As-needed-only ICS-SABA

Combination as-needed ICS-SABA

- BEST study, combination BDP-albuterol *(Papi et al, NEJMed 2007, n=445, 6 months)*
  - Mean number of exacerbations per patient per year lower with as-needed combination (0.74) and regular BDP (0.71) compared with as-needed albuterol (1.63, P<0.001) and regular combination BDP-albuterol (1.76, P<0.001)

Taking ICS whenever SABA taken with separate inhalers

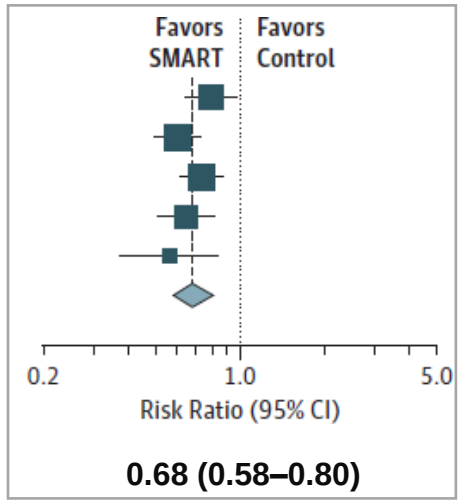
- TREXA study, BDP and albuterol, children and adolescents *(Martinez et al, Lancet 2011, n=288, 9 months)*
  - Frequency of exacerbations highest with albuterol alone (49%); lower with daily BDP (28%, p=0.03), daily plus as-needed BDP and SABA (31%, p=0.07) and as-needed BDP+SABA (35%, p=0.07)
  - Growth 1.1cm less in daily and combined groups but not as-needed-only group
- BASALT study, BDP and albuterol, adults *(Calhoun et al, JAMA 2012, n=342, 9 months)*
  - Similar exacerbations with as-needed BDP+SABA as with 6-weekly physician-adjusted or FeNO-adjusted ICS
- ASIST study, BDP and albuterol, African-American children and adolescents *(Sumino et al, Annals ATS 2020, n=206, 12 months)*
  - Similar symptoms control and exacerbations compared with physician-adjusted ICS

BDP: beclometasone dipropionate; ICS: inhaled corticosteroids; SABA: short-acting beta2-agonists

Evidence: Steps 3–5

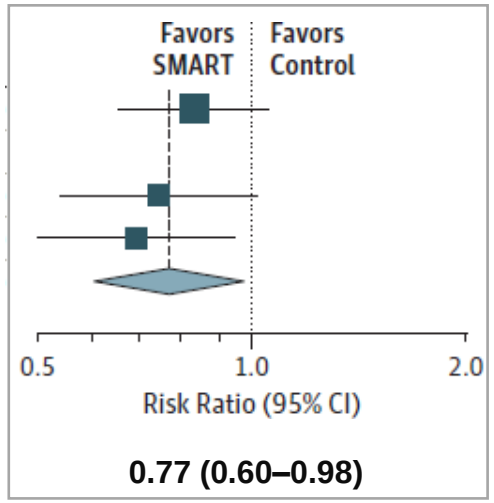
Track 1, Steps 3–5: Maintenance and reliever therapy (MART)

- MART with ICS-formoterol reduces severe exacerbations compared with ICS or ICS-LABA plus SABA reliever, with similar symptom control
  - Confirmed by regulatory studies and pragmatic open-label studies, n~30,000
- Both budesonide and formoterol contribute to the reduction in severe exacerbations

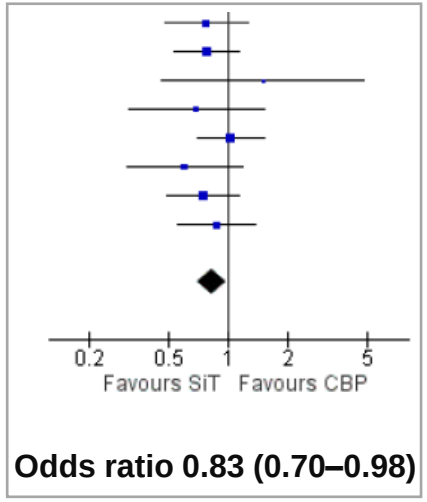


Compared with same dose ICS-LABA +SABA

Sobieraj et al, JAMA 2018 (n=22,748)

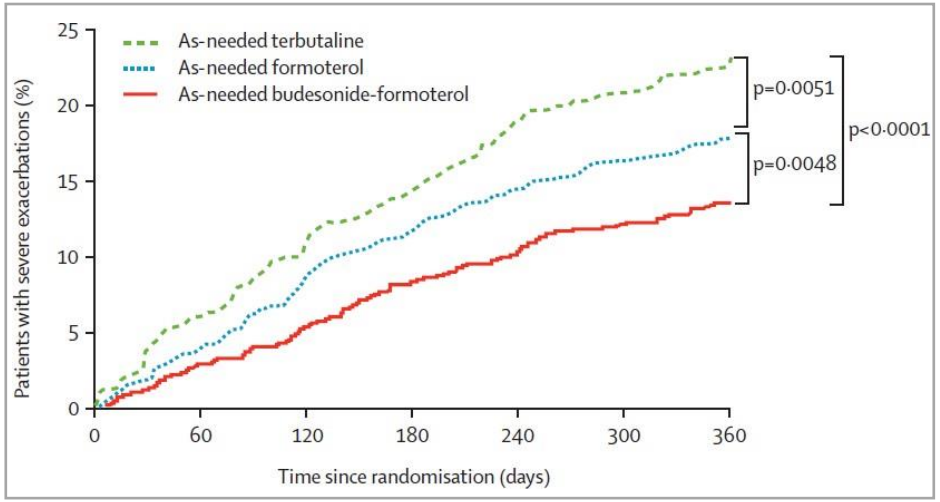


Compared with higher dose ICS-LABA + SABA



Compared with conventional best practice

Cates et al, Cochrane 2013 (n=4,433)



Compared with formoterol or SABA reliever

Rabe, Lancet 2006
N=3,395, all taking maintenance budesonide-formoterol

Track 2, Steps 3–5: as-needed ICS-SABA added to maintenance treatment

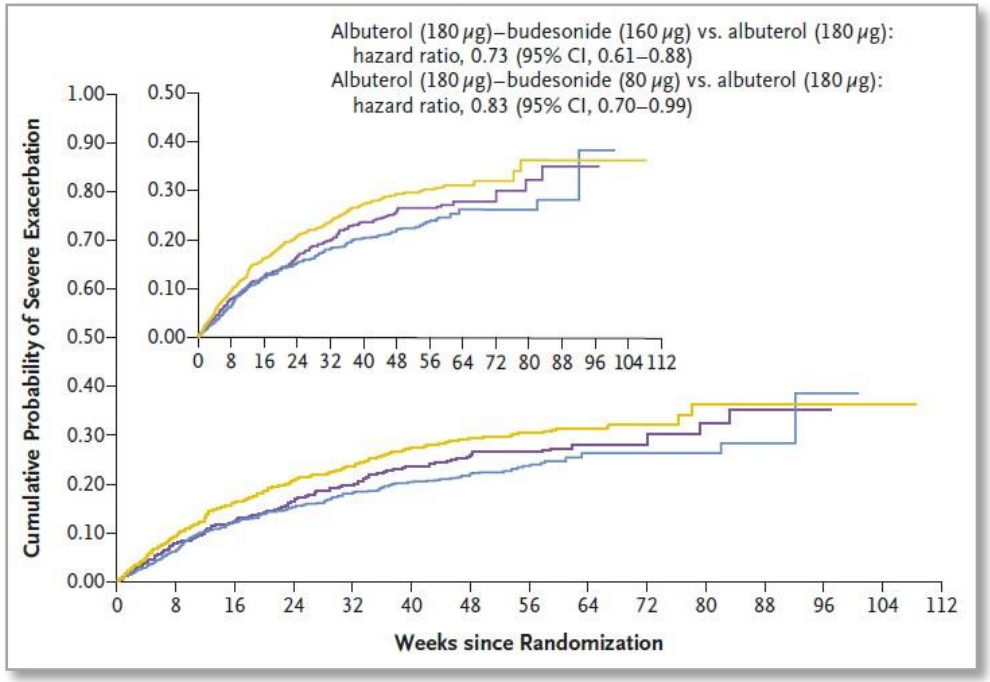

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

Papi et al, NEJMed 2022 (n=3,132)



In patients taking Step 3–5 maintenance treatment:

- Hazard ratio for probability of severe exacerbations was 0.73 (95% CI 0.61–0.88) with higher dose of as-needed albuterol-budesonide compared with as-needed albuterol
- Most benefit seen in Step 3

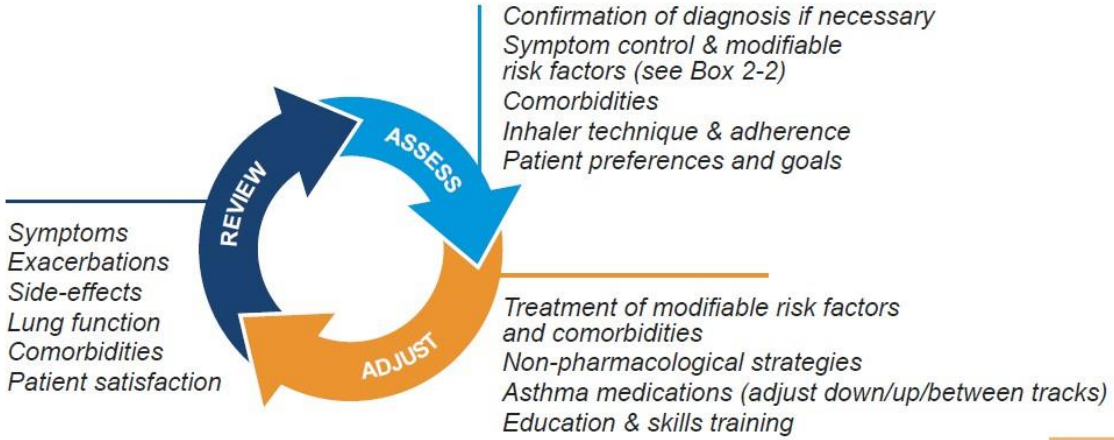
From "Albuterol-Budesonide Fixed Dose Combination Rescue Inhaler for Asthma", Papi et al, NEJMed 2022; 386:2071-2083 Copyright © 2023. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Why is GINA Track 1 with ICS-formoterol preferred?

- **Steps 1–2**: weight of evidence for effectiveness and safety compared with SABA alone, or low-dose ICS plus as-needed SABA (4x12 month studies, n~10,000) *(Crossingham et al, Cochrane 2021)*
  - As-needed ICS-SABA: only one 6-month RCT (n=455) *(Papi et al, NEJMed 2007)*
- **Steps 3–5**: weight of evidence for effectiveness and safety of MART versus regimens with as-needed SABA (n~30,000) *(Sobieraj et al, JAMA 2018; Cates et al, Cochrane 2013)*
  - As-needed ICS-SABA: only one RCT (n=3,132) vs as-needed SABA *(Papi et al, NEJMed 2022);* cannot be used for maintenance and reliever therapy
- Both the ICS and the formoterol contribute to reduction in severe exacerbations *(Tattersfield et al, Lancet 2001; Pauwels et al, ERJ 2003; Rabe et al, Lancet 2006)*
  - Safety established up to total 12 inhalations in any day, in large studies
- **Simplicity of approach** for patients and clinicians
  - A single medication for both symptom relief and maintenance treatment (if needed) from diagnosis
  - Avoids confusion about inhaler technique with different devices
  - Short-term increase in symptoms → patient increases the number of **as-needed** doses
  - Step treatment down or up by changing the number of maintenance doses

GINA 2023 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



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Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol*			

See GINA severe asthma guide

TRACK 2: Alternative **CONTROLLER and RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: as-needed ICS-SABA*, or as-needed SABA				

Other controller options (limited indications, or less evidence for efficacy or safety – see text)	*Low dose ICS whenever SABA taken*, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory reliever (AIR)

How to prescribe low-dose ICS-formoterol in GINA Track 1

Example: budesonide-formoterol 200/6 mcg [160/4.5 delivered dose]

- **Steps 1–2**: take 1 inhalation whenever needed for symptoms
- **Step 3**: take 1 inhalation twice a day (or once a day) PLUS 1 inhalation whenever needed for symptoms
- **Steps 4–5**: take 2 inhalations twice a day PLUS 1 inhalation whenever needed for symptoms
- As-needed doses of ICS-formoterol can also be taken before exercise *(Lazarinis et al, Thorax 2014)* or before allergen exposure *(Duong et al, JACI 2007)*

See following slides for medications, doses, and maximum number of inhalations in any day for GINA Track 1

Step	Age (years)	Medication and device (check patient can use inhaler)	Metered dose (mcg/inhalation)	Delivered dose (mcg/inhalation)	Dosage
Steps 1–2 (AIR-only)	6–11	(No evidence)	-	-	-
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**1 inhalation whenever needed**
Step 3 MART	6–11	Budesonide-formoterol DPI	100/6	80/4.5	**1 inhalation once daily**, PLUS 1 inhalation whenever needed
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**1 inhalation once or twice daily,** PLUS 1 inhalation whenever needed
	≥18	BDP-formoterol pMDI	100/6	84.6/5.0	
Step 4 MART	6–11	Budesonide-formoterol DPI	100/6	80/4.5	**1 inhalation twice daily**, PLUS 1 inhalation whenever needed
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**2 inhalations twice daily**, PLUS 1 inhalation whenever needed
	≥18	BDP-formoterol pMDI	100/6	84.6/5.0	
Step 5 MART	6–11	(No evidence)	-	-	-
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**2 inhalations twice daily**, PLUS 1 inhalation whenever needed
	≥18	BDP-formoterol pMDI	100/6	84.6/5.0	

DPI: dry powder inhaler; pMDI: pressurized metered dose inhaler. For budesonide-formoterol pMDI with 3 mcg [2.25 mcg] formoterol, use double number of puffs

Step	Age (years)	Medication and device (check patient can use inhaler)	Metered dose (mcg/inhalation)	Delivered dose (mcg/inhalation)	Dosage
Steps 1–2 (AIR-only)	6–11	(No evidence)	-	-	-
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**1 inhalation whenever needed**

DPI: dry powder inhaler; pMDI: pressurized metered dose inhaler. For budesonide-formoterol pMDI with 3 mcg [2.25 mcg] formoterol, use double number of puffs

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	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**1 inhalation once or twice daily,** PLUS 1 inhalation whenever needed
	≥18	BDP-formoterol pMDI	100/6	84.6/5.0	
Step 4 MART	6–11	Budesonide-formoterol DPI	100/6	80/4.5	**1 inhalation twice daily**, PLUS 1 inhalation whenever needed
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**2 inhalations twice daily**, PLUS 1 inhalation whenever needed
	≥18	BDP-formoterol pMDI	100/6	84.6/5.0	

DPI: dry powder inhaler; pMDI: pressurized metered dose inhaler. For budesonide-formoterol pMDI with 3 mcg [2.25 mcg] formoterol, use double number of puffs

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Step 5 MART	6–11	(No evidence)	-	-	-
	12–17 ≥18	Budesonide-formoterol DPI	200/6	160/4.5	**2 inhalations twice daily**, PLUS 1 inhalation whenever needed
	≥18	BDP-formoterol pMDI	100/6	84.6/5.0	

DPI: dry powder inhaler; pMDI: pressurized metered dose inhaler. For budesonide-formoterol pMDI with 3 mcg [2.25 mcg] formoterol, use double number of puffs

Reliever doses of ICS-formoterol - how much can be taken?

- For ICS-formoterol with 6 mcg (4.5 mcg delivered dose) of formoterol, take **1 inhalation** whenever needed for symptom relief
- Another inhalation can be taken after a few minutes if needed
- Maximum total number of inhalations in any single day (as-needed + maintenance)
  - **Budesonide-formoterol**: maximum 12 inhalations* for adults, 8 inhalations for children, based on extensive safety data *(Tattersfield et al, Lancet 2001; Pauwels et al, ERJ 2003)*
  - **Beclometasone-formoterol**: maximum total 8 inhalations in any day *(Papi et al, Lancet Respir Med 2013)*
- Emphasize that most patients need far fewer doses than this!

- For pMDIs containing 3 mcg formoterol (2.25 mcg delivered dose), take 2 inhalations each time

**For budesonide-formoterol 200/6 [delivered dose 160/4.5 mcg], 12 inhalations gives 72 mcg formoterol (54 mcg delivered dose)*

Practical advice for GINA Track 1

- At first, patients may be unsure whether ICS-formoterol will work as well as their previous SABA reliever
  - In the PRACTICAL study, 69% patients said ICS-formoterol worked as fast as, or faster than, their previous SABA *(Baggott et al, ERJ 2020)*
  - Suggest to the patient that they try out the new reliever at a convenient time
  - Emphasise that they should use the ICS-formoterol **instead of** their previous SABA, and that they should take an additional inhalation when they have more symptoms
- Advise patients to have two inhalers (if possible), 1 at home, 1 in bag/pocket
- Advise patients to rinse and spit out after maintenance doses, but this is not needed with reliever doses
  - No increased incidence of candidiasis in RCTs with this recommendation (n~40,000)
- Use an action plan customised to MART
  - The patient continues their usual maintenance ICS-formoterol inhalations, but takes more **as-needed** ICS-formoterol inhalations
  - Taking extra as-needed inhalations reduces the risk of progressing to a severe exacerbation needing oral corticosteroids *(Bousquet et al, Respir Med 2007; Buhl et al, Respir Res 2012; O'Byrne et al, Lancet Respir Med 2021)*
- Additional practical advice for MART *(Reddel et al, JACI in Practice 2022)*

Action plan for MART with ICS-formoterol

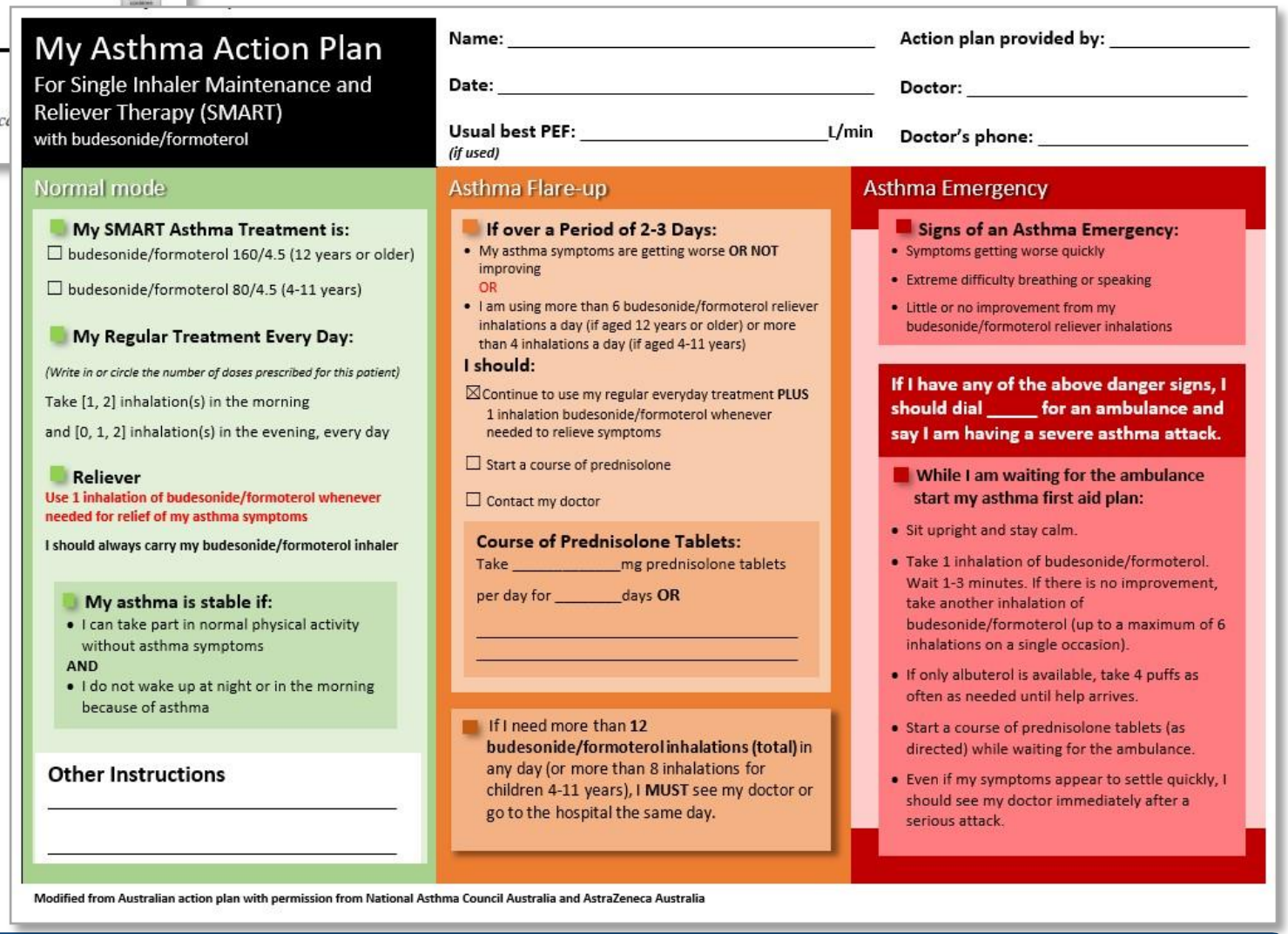
A Practical Guide to Implementing SMART in Asthma Management

Helen K. Reddel, MB, BS, PhD[a,*], Eric D. Bateman, MB, ChB, MD[b,*], Michael Schatz, MD, MS[c], Jerry A. Krishnan, MD, PhD[d], and Michelle M. Cloutier, MD[e] *Sydney, Australia; Cape Town, South Africa; Chicago, Ill; and Farmington, Conn*

Reddel et al, JACI in Practice 2022; 10: S31-s38

This article includes a writable action plan template
That can be modified for other combination ICS-formoterol inhalers, and for as-needed-only ICS-formoterol

For additional action plans with ICS-formoterol reliever, see National Asthma Council Australia Action plan library
www.nationalasthma.org.au/health-professionals/asthma-action-plans



My Asthma Action Plan
For Single Inhaler Maintenance and Reliever Therapy (SMART)
with budesonide/formoterol

Name: _____ Action plan provided by: _____
Date: _____ Doctor: _____
Usual best PEF: _____ L/min (if used) Doctor's phone: _____

Normal mode

My SMART Asthma Treatment is:
☐ budesonide/formoterol 160/4.5 (12 years or older)
☐ budesonide/formoterol 80/4.5 (4-11 years)

My Regular Treatment Every Day:
(Write in or circle the number of doses prescribed for this patient)
Take [1, 2] inhalation(s) in the morning
and [0, 1, 2] inhalation(s) in the evening, every day

Reliever
Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms
I should always carry my budesonide/formoterol inhaler

My asthma is stable if:
- I can take part in normal physical activity without asthma symptoms

AND
- I do not wake up at night or in the morning because of asthma

Other Instructions
_____
_____

Asthma Flare-up

If over a Period of 2-3 Days:
- My asthma symptoms are getting worse **OR NOT** improving

OR
- I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years or older) or more than 4 inhalations a day (if aged 4-11 years)

I should:
☒ Continue to use my regular everyday treatment **PLUS** 1 inhalation budesonide/formoterol whenever needed to relieve symptoms
☐ Start a course of prednisolone
☐ Contact my doctor

Course of Prednisolone Tablets:
Take _____mg prednisolone tablets per day for _____days **OR**
_____
_____

If I need more than **12 budesonide/formoterol inhalations (total)** in any day (or more than 8 inhalations for children 4-11 years), I **MUST** see my doctor or go to the hospital the same day.

Asthma Emergency

Signs of an Asthma Emergency:
- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from my budesonide/formoterol reliever inhalations

If I have any of the above danger signs, I should dial _____ for an ambulance and say I am having a severe asthma attack.

While I am waiting for the ambulance start my asthma first aid plan:
- Sit upright and stay calm.
- Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement, take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion).
- If only albuterol is available, take 4 puffs as often as needed until help arrives.
- Start a course of prednisolone tablets (as directed) while waiting for the ambulance.
- Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack.

Modified from Australian action plan with permission from National Asthma Council Australia and AstraZeneca Australia

Supplement to Reddel et al, JACI in Practice 2022; 10: S31-s38

This template can be modified for other ICS-formoterol combinations or for as-needed-only ICS-formoterol.
The action plan on which it is based has been widely used in Australia and other countries since 2007.

My Asthma Action Plan

For Single Inhaler Maintenance and Reliever Therapy (SMART)
with budesonide/formoterol

Name: _____ **Action plan provided by:** _____

Date: _____ **Doctor:** _____

Usual best PEF: _____ L/min *(if used)* **Doctor's phone:** _____

Normal mode

My SMART Asthma Treatment is:

☐ budesonide/formoterol 160/4.5 (12 years or older)

☐ budesonide/formoterol 80/4.5 (4-11 years)

My Regular Treatment Every Day:

(Write in or circle the number of doses prescribed for this patient)

Take [1, 2] inhalation(s) in the morning

and [0, 1, 2] inhalation(s) in the evening, every day

Reliever

Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms

I should always carry my budesonide/formoterol inhaler

My asthma is stable if:

- I can take part in normal physical activity without asthma symptoms

AND

- I do not wake up at night or in the morning because of asthma

Other Instructions

_____

_____

Asthma Flare-up

If over a Period of 2-3 Days:

- My asthma symptoms are getting worse **OR NOT** improving

OR

- I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years or older) or more than 4 inhalations a day (if aged 4-11 years)

I should:

☒ Continue to use my regular everyday treatment **PLUS** 1 inhalation budesonide/formoterol whenever needed to relieve symptoms

☐ Start a course of prednisolone

☐ Contact my doctor

Course of Prednisolone Tablets:

Take _____mg prednisolone tablets

per day for _____days **OR**

_____

_____

If I need more than **12 budesonide/formoterol inhalations (total)** in any day (or more than 8 inhalations for children 4-11 years), I **MUST** see my doctor or go to the hospital the same day.

Asthma Emergency

Signs of an Asthma Emergency:

- Symptoms getting worse quickly
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- Little or no improvement from my budesonide/formoterol reliever inhalations

If I have any of the above danger signs, I should dial _____ for an ambulance and say I am having a severe asthma attack.

While I am waiting for the ambulance start my asthma first aid plan:

- Sit upright and stay calm.
- Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement, take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion).
- If only albuterol is available, take 4 puffs as often as needed until help arrives.
- Start a course of prednisolone tablets (as directed) while waiting for the ambulance.
- Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack.

GINA 2023 – Children 6–11 years

Personalized asthma management:
Assess, Adjust, Review

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Child and parent/caregiver preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Child (and parent/ caregiver) satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

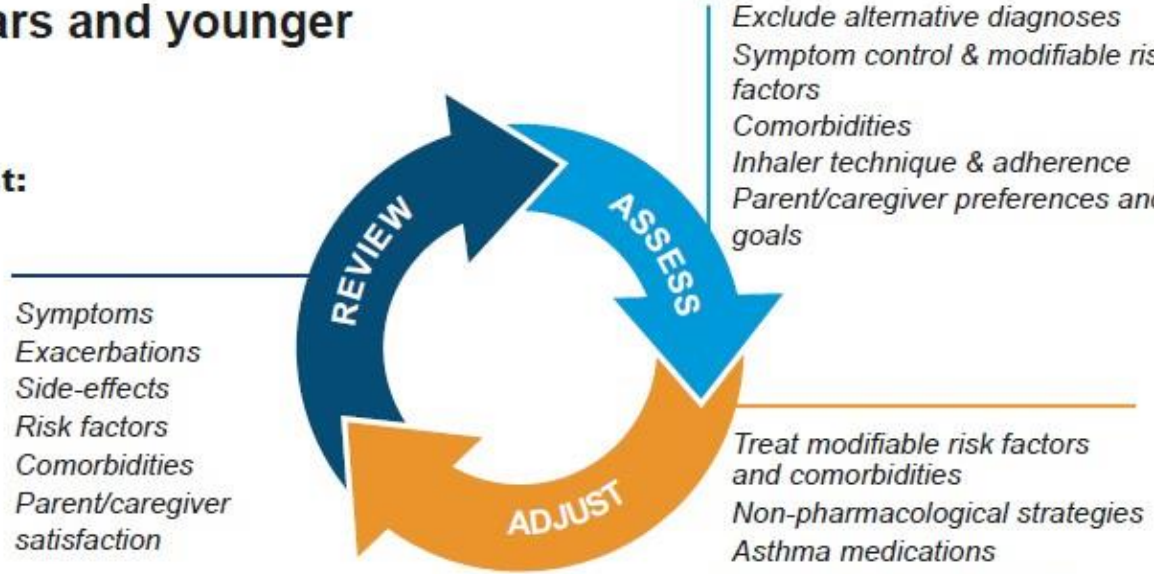
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4Rα, anti-IL5
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken**	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*As last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed SABA (or ICS-formoterol reliever* in MART in Steps 3 and 4)				

*Anti-inflammatory relievers (AIR)

GINA 2023 – Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



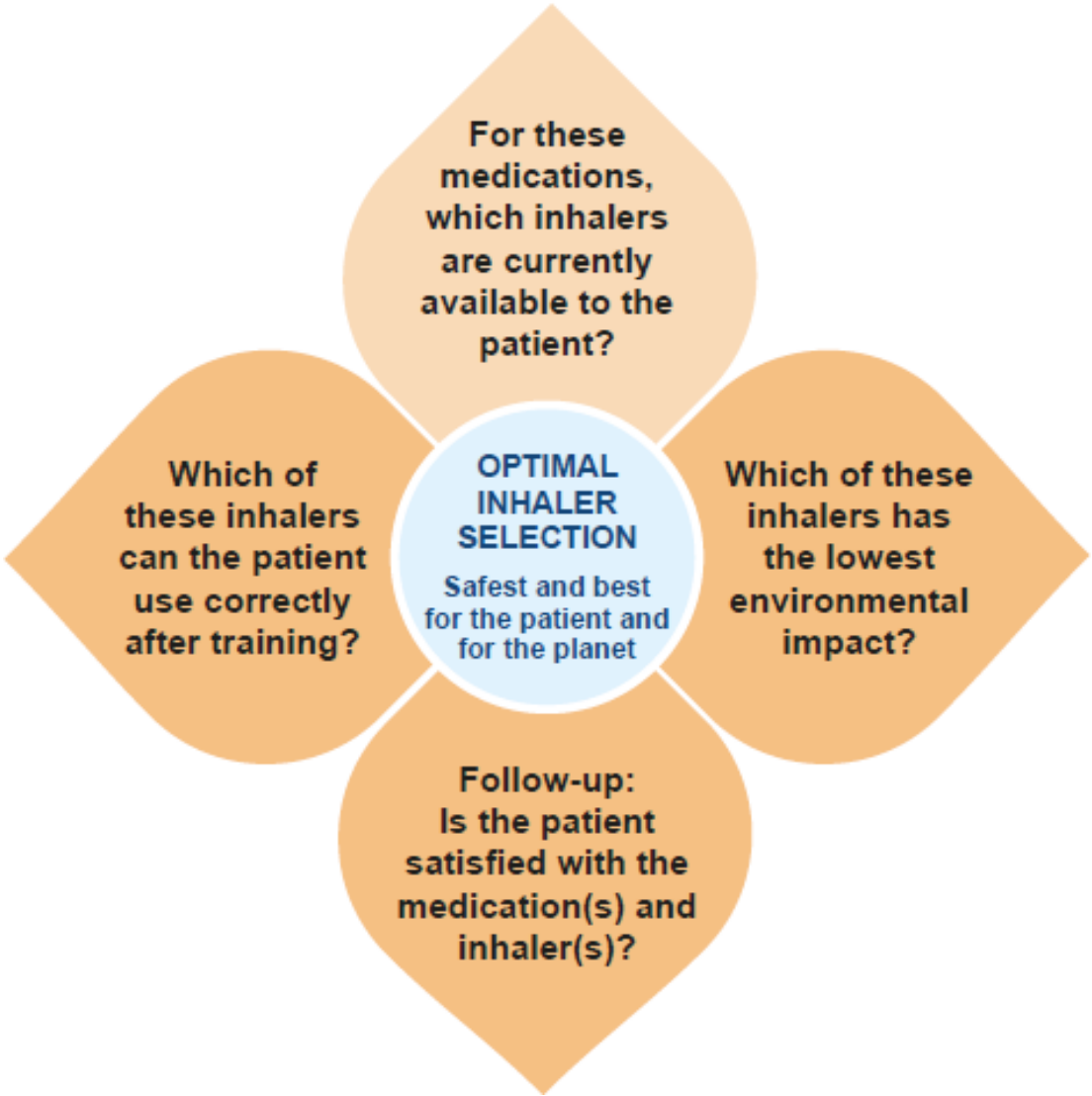
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE	*(Insufficient evidence for daily controller)*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS *(See Box 6-7)*	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

Inhaler choice and environmental considerations

- Inhaled corticosteroids markedly reduce the risk of asthma exacerbations and death
  - But limited availability and access in low and middle income countries
- Many inhaler types available, with different techniques
- Some inhalers are not suitable for some patients. For example:
  - DPIs are not suitable for children ≤5 years and some elderly
  - pMDIs difficult for patients with arthritis or weak muscles
  - Capsule devices are difficult for patients with tremor
- Most patients don't use their inhaler correctly
  - More than one inhaler → more errors
- Incorrect technique → more symptoms → worse adherence → more exacerbations → higher environmental impact
- Propellants in current pMDIs have 25x global warming potential compared with dry powder inhalers
  - New propellants are being developed but not yet approved
- Choice of inhaler is important!

For this patient, which is the right class of medication?



Inhaler choice and environmental considerations

- First, what is the right medication for this patient?
  - Control symptoms and reduce exacerbations
  - Urgent healthcare and hospitalization have a heavy environmental burden
- Which inhaler(s) can the patient access for this medication?
  - Low/middle income countries often have limited choice and access
  - Cost of inhalers is a major burden
- Which of these inhalers can the patient use correctly?
  - Incorrect technique → more exacerbations
- What are the environmental implications of these inhaler(s)?
  - Manufacture
  - Propellant (for pMDIs)
  - Recycling potential
- Is the patient satisfied with the treatment and the inhaler?
  - Consider the patient's environmental priorities
  - Avoid 'green guilt', which may contribute to poor adherence
  - Check inhaler technique frequently

Difficult-to-treat and severe asthma

- Changes in GINA 2023
  - Double-blind study of withdrawal of mepolizumab in adults with severe eosinophilic asthma found more exacerbations in those who ceased mepolizumab than those who continued treatment *(Moore et al, ERJ 2022)*
  - Mepolizumab (anti-IL5) added as a Step 5 option for children 6–11 years with severe eosinophilic asthma *(Jackson et al, Lancet 2022)*
- Regardless of regulatory approvals, GINA recommends biologic therapy for asthma **only** if asthma is severe, and **only** if treatment has been optimized
- Head-to-head studies are needed
- Non-asthma indications for biologic therapy are mentioned only if the condition is relevant to asthma management, or if it is commonly associated with asthma
- Severe asthma guide published mid-2023 in large format

Other changes

- Pulse oximetry: FDA safety communication
  - Potential overestimation of oxygen saturation in people with dark skin color
- Risk of drug interactions between salmeterol or vilanterol and ritonavir-boosted nirmatrelvir (NMV/r)
  - Risk of cardiovascular adverse effects *(Carr et al, JACI 2023; 151: 809-817)*
  - Drug interaction websites recommend cessation of the LABA for duration of treatment, without warning about risks
  - Options (if available): prescribe alternative antiviral therapy, or switch to ICS or ICS-formoterol for duration of therapy plus 5 days. Remember to teach correct technique if prescribing a new inhaler
  - (ICS effects unlikely given short duration of treatment)
- FeNO-guided treatment: well-conducted multinational study in children found no reduction in exacerbations *(Turner et al, Lancet Respir Med 2022)*. Update of Cochrane reviews awaited
- Updated advice about describing asthma severity
  - Consider using the term ‘apparently mild asthma’ in health professional education: patients with apparently mild asthma can still have severe or fatal asthma exacerbations
- See GINA report for full list of changes

Global priorities for asthma management

Improving lung health in low-income and middle-income countries: from challenges to solutions

Jamilah Meghji, Kevin Mortimer*, Alvar Agusti, Brian W Allwood, Innes Asher, Eric D Bateman, Karen Bissell, Charlotte E Bolton, Andrew Bush, Bartolome Celli, Chen-Yuan Chiang, Alvaro A Cruz, Anh-Tuan Dinh-Xuan, Asma El Sony, Kwun M Fong, Paula I Fujiwara, Mina Gaga, Luis Garcia-Marcos, David M G Halpin, John R Hurst, Shamanthi Jayasooriya, Ajay Kumar, Maria V Lopez-Varela, Refiloe Masekela, Bertrand H Mbatchou Ngahane, Maria Montes de Oca, Neil Pearce, Helen K Reddel, Sundeep Salvi, Sally J Singh, Cherian Varghese, Claus F Vogelmeier, Paul Walker, Heather J Zar, Guy B Marks*

Lancet 2021

J Pan Afr Thorac Soc 2022

The reality of managing asthma in sub-Saharan Africa – Priorities and strategies for improving care

Kevin Mortimer[1], Refiloe Masekela[2], Obianuju B Ozoh[3], Eric Donn Bateman[4], Rebecca Nantanda[5], Arzu A. Yorgancıoğlu[6], Jeremiah Chakaya[7], Helen K. Reddel[8]

Asthma management in low and middle income countries: case for change

Kevin Mortimer[1,2], Helen K. Reddel[3], Paulo M. Pitrez[4] and Eric D. Bateman[5]

ERJ 2022

Int J Tuberc Lung Dis 2022

Improving access to affordable quality-assured inhaled medicines in low- and middle-income countries

M. Stolbrink,[1,2] M. J. Chinouya,[3] S. Jayasooriya,[4] R. Nightingale,[1,5] L. Evans-Hill,[6] K. Allan,[7] H. Allen,[8] J. Balen,[9] T. Beacon,[10] K. Bissell,[11] J. Chakaya,[1,12] C-Y. Chiang,[13,14,15] M. Cohen,[16] G. Devereux,[1] A. El Sony,[17] D. M. G. Halpin,[18] J. R. Hurst,[19] C. Kiprop,[5] A. Lawson,[20] C. Macé,[13] A. Makhanu,[5] P. Makokha,[5] R. Masekela,[21] H. Meme,[22] E. M. Khoo,[23,24] R. Nantanda,[25] S. Pasternak,[26] C. Perrin,[13] H. Reddel,[27,28] S. Rylance,[29] P. Schweikert,[20] C. Were,[26] S. Williams,[24] T. Winders,[30] A. Yorgancioglu,[31,32] G. B. Marks,[13,33] K. Mortimer[13,34]