

# Asthma treatment in children: A pragmatic approach

R Masekela,<sup>1</sup> PhD; A Jeevanathrum,<sup>2</sup> Cert Pulmonology (SA) Paed; S Kling,<sup>3</sup> FCPaed (SA), MPhil (Appl Ethics);  
T C Gray,<sup>3</sup> Cert Pulmonology (SA) Paed; J Morrison,<sup>3</sup> Cert Pulmonology (SA) Paed; A Vanker,<sup>4</sup> Cert Pulmonology (SA) Paed;  
A S Puterman,<sup>5</sup> FC Paed (SA); D Rhode,<sup>6</sup> Cert Pulmonology (SA) Paed; E W Zöllner,<sup>3</sup> PhD; P de Waal,<sup>7</sup> MMed (Paed);  
A I Manjra,<sup>8</sup> FCPaed (SA), M Clin Pharm; M Levin,<sup>4</sup> PhD; H Zar,<sup>4</sup> PhD; R J Green,<sup>2</sup> PhD, DSc; F E Kritzinger,<sup>3,9</sup> Cert Pulmonology (SA) Paed;  
on behalf of the South African Childhood Asthma Working Group (SACAWG)

<sup>1</sup> Inkosi Albert Luthuli Central Hospital and Department of Paediatrics and Child Health, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

<sup>2</sup> Steve Biko Academic Hospital and Department of Paediatrics and Child Health, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa

<sup>3</sup> Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

<sup>4</sup> Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, and Medical Research Council Unit on Child and Adolescent Health, Faculty of Health Sciences, University of Cape Town, South Africa

<sup>5</sup> Private practice, Life Kingsbury Hospital, Cape Town, South Africa

<sup>6</sup> Private practice, Melomed Private Hospital, Cape Town, South Africa

<sup>7</sup> Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

<sup>8</sup> Private practice, Life Westville Hospital, Durban, South Africa

<sup>9</sup> Netcare Christiaan Barnard Memorial Hospital, Cape Town, South Africa

**Corresponding author:** R Masekela (masekelar@ukzn.ac.za)

**Background.** Asthma is a heterogeneous condition characterised by chronic inflammation and variable expiratory airflow limitation, with airway reversibility. Management of chronic inflammation with anti-asthma medication improves asthma control and quality of life.

**Objectives.** To provide an evidence-based approach for chronic asthma management in young children and adolescents and provide guidance on the use of new asthma drugs in children.

**Methods.** The South African Childhood Asthma Working Group (SACAWG) convened in January 2017. The asthma treatment task group reviewed the available scientific literature and international asthma treatment guidelines. The evidence was then graded according to the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system and recommendations were made based on scientific evidence and local context. Asthma management recommendations were made for children <6 years of age and older children and adolescents, as well as for stepping up and stepping down of therapy. This review does not include biologics or novel asthma drugs, which are covered in another CME article in this edition of SAMJ.

**Conclusions.** To ensure good response, treatment and adherence, type of medication, device and checking of technique are all critical. Stepping up of therapy should be done only after ensuring good adherence and technique. Once therapeutic response is achieved, medication administration has to be stepped down to improve ease of use and avoid unnecessary side-effects.

*S Afr Med J* 2018;108(8):612-618. DOI:10.7196/SAMJ.2018.v108i8.13164

The South African Childhood Asthma Working Group (SACAWG), a subcommittee of the Allergy Society of South Africa (ALLSA), first published its guideline for the management of chronic asthma in children and adolescents in 1992, followed by revisions in 1994,<sup>[1]</sup> 2000<sup>[2]</sup> and 2009.<sup>[3]</sup> 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 and new drug-delivery devices).

Pharmacotherapy is the cornerstone of asthma management. Selection of medication and delivery devices has to meet the patients' needs and characteristics. Periodic assessment of asthma control and review of management are critical to gain control of the disease and limit medication side-effects.

## Methods

SACAWG reconvened in January 2017 with 6 task groups, each headed by a leader (Appendix A), constituting the editorial committee on assessment of asthma epidemiology, diagnosis, control, treatments, novel treatments and self-management plans. The asthma medication

task groups were charged with the responsibility of reviewing the available scientific literature and assigning evidence levels according to the methodology used in current guideline documents. PubMed and Google Scholar searches were done to review the current level of evidence since the publication of the previous guideline.<sup>[3]</sup> The level of evidence and key recommendations were graded (Appendix B) according to the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system. After completion of each sub-section, it was sent to the entire working group for review, comment and revision. Any disagreements or inconsistencies were dealt with via round robin, with a majority recommendation based on the evidence if there was disagreement.

## Assessment of severity to initiate therapy

The method of assessment conforms to international assessment criteria. The assessment of severity is used to assign a child to a particular treatment group as a starting point. This assessment refers to a child's symptoms and lung function (peak expiratory flow (PEF)

or forced expiratory flow in 1 second (FEV<sub>1</sub>)) between acute episodes if they are not receiving long-term therapy (Table 1). Severity can also be measured once asthma control is achieved by the step of care (i.e. various medications) required to maintain control. One or more features must be present to assign a severity grading to the most severe grade in which any feature occurs.

### Principles of medication

When selecting medication for an asthmatic patient, the following principles apply: regular anti-inflammatory medication is indicated for persistent asthma, but inhaled therapy is preferable, especially inhaled bronchodilators and inhaled steroids.

Drugs are classified as:

- **Relievers (bronchodilators)** for acute relief from symptoms, including inhaled short-acting beta<sub>2</sub>-agonists (SABAs) (evidence level I) and anticholinergics. Short-acting xanthines are *not* recommended in the maintenance treatment of asthma. Anticholinergics are less potent, have a slower onset of action (30 - 60 minutes) and can be used during exacerbations.
- **Controllers (anti-inflammatory drugs)** for long-term control may modify airway inflammation that is characteristic of asthma.

Inhaled corticosteroids (ICSs) are the most effective controller therapy for asthma (evidence level I). Leukotriene receptor antagonists (LTRAs) are anti-inflammatories that exert their effects via different pathways than ICSs. Long-acting beta<sub>2</sub>-agonists (LABAs) have weak anti-inflammatory effects. Slow-release theophyllines also have weak anti-inflammatory effects at lower doses than those required for bronchodilation.

A number of different ICS preparations are available in South Africa (SA) (Tables 2 and 3). ICSs are usually administered twice daily, but budesonide and ciclesonide (registered only for children >12 years old) are approved for once-daily use in children with mild asthma. Most children >5 years of age are controlled on low daily doses of ICSs (100 - 200 µg budesonide or equivalent). Wheezing caused by viral infections is very common in children <2 years of age and often resolves spontaneously or remits with increasing age. ICSs should only be used if symptoms are particularly troublesome, and if there is a need for admission and oxygen therapy, with a clear response to treatment. Most importantly, the administration of ICSs should be discontinued if there is no response or a poor response.

**Table 1. Classification of asthma severity based on symptoms and lung function (presenting for the first time without treatment)**

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

PEF = peak expiratory flow; PEFR = peak expiratory flow rate.  
\*Applicable to children >5 years old.

**Table 2. Preferred low-dose ICS in children <5 years old\***

ICS	Total daily inhaled dose, µg
Beclomethasone dipropionate (HFA)	100
Budesonide (pMDI and spacer) <sup>†</sup>	200
Budesonide (nebulised) <sup>†</sup>	500
Fluticasone propionate (HFA)	100

ICS = inhaled corticosteroid; HFA = hydrofluoroalkane; pMDI = pressurised metered-dose inhaler.  
\*Adapted from Global Initiative for Asthma.<sup>[4]</sup>  
<sup>†</sup>Most preparations are registered for twice-daily use, except budesonide, which may be administered once daily.

LABAs should *only* be used in combination with an ICS. LABAs are primarily indicated as add-on therapy in children >5 years of age, whose asthma is not controlled by moderate doses of ICSs (evidence level II) (Table 4).

LTRAs have a rapid onset of action (1 - 3 hours) and are taken once a day. They are available in 5 mg tablets, 4 mg chewable tablets and 4 mg oral granule formulations. Because of easy administration (compared with inhaler devices) and once-daily dosing, patients are often adherent to LTRAs only. It should be noted and explained to parents that LTRAs are not the preferred first-line treatment for asthma. LTRAs have been shown to be inferior to ICSs with regard

**Table 3. Estimated equipotent daily dosage of ICS for children 6 - 11 years old**

Drug	Low daily dose, µg	Medium daily dose, µg	High daily dose, µg
Beclomethasone dipropionate CFC	100 - 200	200 - 400	>400
Budesonide DPI	100 - 200	200 - 400	>400
Ciclesonide HFA*	80	80 - 160	>160
Fluticasone propionate HFA <sup>†</sup>	100 - 200	200 - 500	>500
Mometasone furoate	110	220 - <440	≥440
<b>Adolescents (≥12 years old)</b>			
Beclomethasone dipropionate HFA	100 - 200	>200 - 400	>400
Budesonide DPI	200 - 400	>400 - 800	>800
Ciclesonide HFA	80 - 160	>160 - 320	>320
Fluticasone propionate HFA <sup>†</sup>	100 - 250	>250 - 500	>500
Fluticasone furoate <sup>‡</sup>	-	-	-
Mometasone furoate	110 - 220	>220 - 440	>440

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane.  
\*Ciclesonide is registered for children ≥12 years old.  
<sup>†</sup>May be used at half the dose of budesonide equivalent.  
<sup>‡</sup>Equivalent doses unknown.

**Table 4. Combination products available in South Africa\***

Combination	Device	Dose, µg
Fluticasone propionate/ salmeterol	DPI (Accuhaler)	100/50
		250/50
		500/50
Fluticasone propionate/ 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
Fluticasone furoate/ vilanterol <sup>†</sup>	pMDI	100/25
		100/25
Mometasone furoate/ formoterol fumarate	pMDI	100/5
		200/5

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

\*Adapted from Global Initiative for Asthma<sup>[4]</sup> and Hossny *et al.*<sup>[5]</sup>

<sup>†</sup>Indicated only for children ≥12 years old.

to symptom improvement, exacerbation decrease and hospitalisation frequency in the treatment of asthma in the preschool child. This medication may be used as add-on therapy in children >5 years of age, whose asthma is insufficiently controlled by low doses of ICSs (evidence level II), or as alternative first-line therapy to ICSs for episodic or mild persistent asthma in children <5 years old (evidence level II).

Theophylline may be used as add-on therapy in more severe asthma that is not controlled with ICSs in children >12 years of age and in adults (evidence level IV), but safety concerns preclude its recommendation.

Oral corticosteroids should only be used for acute asthma exacerbations, preferably only in hospitalised patients and for a maximum of 3 days at 0.5 - 1 mg/kg/dose of prednisone given once daily. For children <5 years old, these are only recommended in exacerbations that require hospitalisation.

## Routes of administration

### Inhaled medications

Inhaled therapy is the cornerstone of asthma treatment for all children. Most children can be taught to use inhaled therapy effectively. Different age groups require different inhaler devices together with a pressurised metered-dose inhaler (pMDI) with or without a holding chamber (spacer). The alternative is a dry powder metered-dose inhaler (DPI) (Box 1). Considerations when choosing an inhaler device include the efficacy of drug delivery, cost, safety, ease of use, convenience and efficacy in a specific age group.<sup>[5]</sup> A pMDI with holding chamber (spacer) is preferable to nebulised therapy owing to convenience, more effective lung deposition, fewer side-effects and lower cost.<sup>[6-8]</sup> The technique for each device type varies, has to be correct for optimal drug delivery and should be checked at each visit (Box 2).

#### Valved holding chamber (spacer)

Valved holding chambers allow inhalation at a normal respiratory rhythm even without synchronising actuation and inhalation, thus increasing inhalation efficiency. Spacers also retain large drug particles that would otherwise be deposited in the oropharynx.

### Box 1. Choice of inhaler device for children

Age group, years	Preferred device
<4	pMDI and spacer with face mask
4 - 6	pMDI and spacer with mouthpiece
>6	Dry powder inhaler, or pMDI with spacer and mouthpiece or breath-actuated pMDI

pMDI = pressurised metered-dose inhaler.

### Box 2. Correct use of pressurised metered-dose inhaler and holding chamber (spacer)

Assemble spacer, remove mouthpiece cover from the pMDI, and attach MDI

Shake canister vigorously for 5 s, then hold assembled canister-spacer/chamber in a horizontal position

Breathe out normally

Place mouthpiece of spacer/chamber into mouth and close lips around mouthpiece\*

At the start of the next inhalation, actuate the pMDI

Keep inhaling deeply and slowly through your mouth. If you hear a whistling sound from the chamber, slow down the rate of inhalation

Hold your breath for 5 - 10 s. Then breathe out slowly and gently<sup>†</sup>

Wait 15 - 30 s before you give the second puff, if required. Shake the inhaler again before the second puff

If the inhaler is a steroid medicine, rinse out your mouth, gargle, and spit out the water

Remove the pMDI from spacer/chamber and replace the mouthpiece cover

pMDI = pressurised metered-dose inhaler.

\*If the spacer has a facemask, hold the latter snugly over the child's mouth and nose.

<sup>†</sup>In a young child who cannot follow instructions, press the pMDI at the start of a slow breath in and keep mask firmly in place for 5 - 6 breaths.

This reduces oropharyngeal side-effects, systemic absorption and bio-availability of inhaled drug. It is especially important for ICSs with first-pass metabolism, such as beclomethasone and budesonide.

#### Nebulisers

A pMDI with a spacer is as effective as, or more effective than, nebulised treatment for acute, severe asthma exacerbation.<sup>[8,9]</sup> Nebulisers have imprecise dosing, are expensive and waste large amounts of drug into the surrounding air. For home use, nebulisers are discouraged; they should be restricted to cases where oxygen administration is necessary and available (evidence level I).

#### Dry powder inhaler

A DPI is a breath-actuated device containing micronised drug particles with a mass median aerodynamic diameter of <5 µm.<sup>[10,11]</sup> DPI devices eliminate the requirement for propellants, as well as for co-ordination between inhalation and device actuation. The disadvantage of DPIs is the high inspiratory flow rates (30 - 120 L/min) that are required to aerosolise the drug.<sup>[11,12]</sup> In one study, the age at which most children who were inexperienced in the use of a DPI could generate a peak inspiratory flow rate of ≥30 L/min was 4 years, and the age at which most children could generate a peak inspiratory flow rate of ≥60 L/min was 9 years.<sup>[12]</sup> Furthermore, the rapid inhalation required to ensure optimal lung deposition might be confusing for children who use both an MDI and a DPI. It should be noted that equivalent doses for these devices also differ.

## Treatment options

Before stepping up of treatment, symptom control, steroid side-effects and comorbid conditions (e.g. allergic rhinitis) must be assessed. Ensure adequate patient education (e.g. inhaler skills, adherence and written asthma action plan). Assess environmental exposure to allergens and irritants, especially tobacco smoke. Consider the possibility of an alternative diagnosis, poor adherence to treatment or incorrect inhaler technique. Do not step up treatment unless the abovementioned problems have been addressed (Tables 5 and 6).

### Step 1: Short-acting beta<sub>2</sub>-agonist as needed

In the case of mild symptoms (not requiring oral corticosteroids and hospital admission with supplemental oxygen), a SABA with a dedicated spacer device, facemask and an adequate technique are indicated. This treatment is reserved for infrequent symptoms and will not prevent future exacerbations.

**Table 5. Asthma treatment options for children 2 - 5 years of age**

Step 1	
Intermittent reliever therapy	SABA as needed
Step 2	
Low-dose controller and as-needed reliever medication	Low-dose ICS Intermittent ICS (second choice if seasonal symptoms) LTRA
Step 3	
Additional controller and as-needed reliever medication	Medium-dose ICS Low-dose ICS and LTRA
Step 4	
Refer to specialist (paediatrician, paediatric allergologist or paediatric pulmonologist)	

SABA = short-acting beta<sub>2</sub>-agonist; ICS = inhaled corticosteroid; LTRA = leukotriene receptor antagonist.

**Table 6. Asthma treatment options for children ≥6 years old**

Step 1	
Intermittent reliever therapy	SABA as needed
Step 2	
Low-dose controller and as-needed reliever medication	Low-dose ICS
Step 3	
Additional controller and as-needed reliever medication	Low-dose ICS/LABA combination therapy (first choice) Medium-dose ICS (second choice)
Step 4	
≥2 controllers and as-needed reliever medication	Low-dose ICS/LABA and LTRA Medium-dose ICS and LABA Tiotropium (>12 years of age) – add to step 3 drugs Theophylline (>12 years of age)
Step 5	
Refer to specialist (paediatrician, paediatric allergologist or paediatric pulmonologist)	

SABA = short-acting beta<sub>2</sub>-agonist; ICS = inhaled corticosteroid; LABA = long-acting beta<sub>2</sub>-agonist; LTRA = leukotriene receptor antagonist.

ICSs should be considered for patients with any of the following asthma-related features:<sup>[14-16]</sup>

- an asthma attack in the past 2 years, requiring the use of bronchodilators and systemic steroids
- using inhaled SABAs ≥3 times a week
- symptomatic ≥3 times a week
- nocturnal waking ≥1 times a week.

### Step 2: Low-dose controller medication and as-needed reliever medication

In all children the preferred option is regular low-dose ICSs, which are the most effective preventer drugs for adolescents and older children for achieving overall treatment goals (evidence level I).<sup>[13-15]</sup> Treatment with low-dose ICSs reduces asthma symptoms, improves lung function and quality of life, and reduces the risk of exacerbations, asthma-related hospitalisations and death (evidence level I).<sup>[13,17,18]</sup>

### Alternative options

In young children with recurrent viral-induced wheezing, regular LTRAs improve some asthma outcomes compared with placebo, but do not reduce the frequency of hospitalisation, courses of prednisone, or number of symptom-free days (evidence level I). As an alternative, LTRAs have some beneficial clinical effects and may be used as initial controller treatment in children unable or unwilling to use ICSs, for patients who experience intolerable side-effects from ICSs or for those with concomitant allergic rhinitis (evidence level II).<sup>[19-23]</sup>

### Intermittent inhaled corticosteroids

For patients with purely seasonal allergic asthma, with no intercurrent asthma symptoms, ICSs should be started immediately when symptoms commence and continued for 4 weeks after the relevant pollen season ends (evidence level IV). Daily ICSs are superior to intermittent ICSs in several indicators of lung function, airway inflammation, asthma control and reliever use. The strength of the evidence means that, currently, equivalence cannot be assumed between the two options and therefore it is recommended to use daily ICSs (evidence level I).<sup>[24]</sup>

### Step 3: Add an additional controller and as-needed reliever medication

A poor response to low-dose ICSs should be escalated to medium-dose ICSs with as-needed SABAs as the preferred treatment option. In children <6 years of age an alternative treatment is medium-dose ICSs or the addition of an LTRA. As an alternative choice, a low-dose ICS/LABA combination with an as-needed SABA can be administered to children >6 years old. To date, evidence shows that the outcomes of these two treatments are similar.<sup>[25,26]</sup> However, meta-analyses demonstrated a trend towards increased risk of exacerbations requiring rescue therapy and hospitalisation with ICS/LABA treatment in children <12 years compared with medium-dose ICSs (evidence level I).<sup>[24-26]</sup> Based on this, it is currently recommended to escalate therapy to medium-dose ICSs as the preferred choice in this age group.

For children ≥12 years of age, the first choice is adding a LABA to a low-dose ICS. There are two strategies for doing this. The traditional approach of combination ICS/LABA therapy with as-needed SABA reliever therapy is well proven to improve asthma control rather than ICSs alone (evidence level I).<sup>[27]</sup> The more recent approach of ICS/formoterol maintenance and reliever therapy (or single-inhaler therapy) may, however, be preferable to traditional fixed-dose ICS/LABA therapy. Studies comparing the two demonstrate a reduced daily

**Box 3. Options for stepping-down treatment in well-controlled asthma\***

Current step	Current medication and dose	Options for stepping down	Evidence level
Step 4	Moderate- to high-dose ICS/LABA	Continue ICS/LABA with 50% reduction in ICS component	II
		Discontinuation of LABA is more likely to lead to deterioration <sup>[40]</sup>	I
	Medium-dose ICS/formoterol as maintenance and reliever	Reduce maintenance ICS/formoterol to low dose, continue as needed with low-dose ICS/formoterol reliever	IV
	High-dose ICS and second controller	Reduce ICS dose by 50% and continue controller <sup>[41]</sup>	II
Step 3	Low-dose ICS/LABA	Reduce ICS/LABA to once-daily dosing	IV
	Low-dose ICS/formoterol as maintenance and reliever	Discontinuation of LABA is more likely to lead to deterioration <sup>[40]</sup>	I
		Reduce maintenance ICS/formoterol dose to once daily and continue as needed with low-dose ICS/formoterol reliever	III
Step 2	Moderate- or high-dose ICS	Reduce ICS dose by 50% <sup>[41]</sup>	I
	Low-dose ICS	Once-daily dosing (budesonide, ciclesonide, mometasone)	I
	Low-dose ICS or LTRA	Consider stopping controller treatment if no symptoms for 6 - 12 months and no risk factors	IV

ICS = inhaled corticosteroid; LABA = long-acting beta<sub>2</sub>-agonist; LTRA = leukotriene receptor antagonist.  
\*Adapted from South African Childhood Asthma Working Group.<sup>[1]</sup>

dose of ICS and a reduced exacerbation rate requiring oral steroids or hospitalisation in the former group (evidence level I).<sup>[27-31]</sup> Of particular importance is that in any age group LABAs should never be used alone and should only be used in combination with an ICS.

The addition of slow-release theophylline to a low-dose ICS has a similar effect as an increase from low- to medium/high-dose ICS (evidence level II).<sup>[32]</sup>

**Step 4: Two or more controllers and as-needed reliever medication**

Other options in this group are switching to high-dose ICSs and adding a second controller, or adding a third controller to a failing medium-dose ICS/LABA regimen. Tiotropium administered by means of a mist inhaler has been demonstrated to improve asthma control in patients who receive medium-dose ICS/LABA therapy and was non-inferior to adding salmeterol to medium/high-dose steroid monotherapy in severe asthma (evidence level I).<sup>[33]</sup> Similarly, the addition of an LTRA<sup>[34-37]</sup> (evidence level II) or slow-release theophylline<sup>[70]</sup> (evidence level II) is efficacious in improving asthma control in severe asthmatics.

Of note is that ICSs have a relatively flat dose-response curve. The main benefits appear to be gained from the use of low- to medium-dose steroids. An increase to high-dose steroids confers little advantage, at the expense of greater side-effects (evidence level I).<sup>[38,39]</sup> Hence, it is generally preferable to add a second or third controller to a failing regimen than increasing the steroid burden.

**Step 5: Refer**

All children with severe asthma who fail appropriate therapy should be referred to a paediatrician, paediatric allergologist or paediatric pulmonologist for further management, also to confirm the diagnosis and exclude aggravating comorbidities.

**Stepping-down treatment**

Stepping-down treatment should be considered once good asthma control has been achieved and maintained for 3 months and lung

function has reached a plateau (evidence level IV). Any step-down treatment depends on patient characteristics, as only a few step-down studies have been performed in children. Approach each step as a therapeutic trial. Provide clear instructions and an asthma action plan. Monitor symptoms and/or PEF and schedule a follow-up visit. Stepping down ICS doses by 25 - 50% at 3-month intervals is feasible and safe for most patients (evidence level I). When stepping down to once-daily dosing, it should preferably be a morning dose. Box 3 summarises step-down strategies for different controller treatments.

**Conclusion**

To ensure a good response from treatment and adherence, the type of medication, device and checking of technique are critical. Stepping up of therapy should be done only after ensuring good adherence and technique. Once therapeutic response is achieved, medication has to be stepped down to improve ease of medication use and avoid unnecessary side-effects.

**Acknowledgements.** We would like to acknowledge the hard work and contribution of the South African Childhood Asthma Working Group (SACAWG) members. We also acknowledge the huge contribution of the late Prof. Cas Motala, who was convener of the past three SACAWG guideline groups. The current guideline was sent to external reviewers and for comment from the Department of Health (Drs Gavin Steele and Jane Ridder) and members of the Allergy Society of South Africa.

**Author contributions.** RM: review, write-up and manuscript writing and editing; FEK, AJ, SK, JM, ASP, DR, PdW, EWZ, TCG, AV: conceptualisation, review, write-up and manuscript editing; and HZ, ML, RJG, AIM: write-up and manuscript editing.

**Funding.** SACAWG conducted a workshop that received an unconditional educational grant from the Allergy Society of South Africa – funded by Novartis.

**Conflicts of interest.** RM: advisory board for AstraZeneca and AbbVie, and speaker for Cipla, AstraZeneca, AbbVie and Novartis. FEK, AJ, SK, JM, ASP, DR, PdW, EWZ, HZ, ML and AIM: none. RJG: advisory board and speaker bureau for AstraZeneca, Aspen/GSK, Cipla, MSD and Novartis.

- South African Childhood Asthma Working Group. Management of chronic childhood and adolescent asthma – 1994 consensus. *S Afr Med J* 1994;84(12):862-866.
- South African Childhood Asthma Working Group. Guideline for the management of chronic asthma in children – 2000 update. *S Afr Med J* 2000;90(5):524-539.
- South African Childhood Asthma Working Group. Management of chronic childhood and adolescent asthma – 2009 update. *S Afr Med J* 2009;9(12):898-912.
- Global Initiative for Asthma. [www.ginasthma.org](http://www.ginasthma.org) (accessed 22 January 2017).
- Hossny E, Rosario N, Lee BW, et al. The use of inhaled corticosteroids in pediatric asthma: Update. *World Allergy Organ J* 2016;9:26. <https://doi.org/10.1186/s40413-016-0117-0>
- Pedersen S. Inhalers and nebulizers: Which to choose and why. *Respir Med* 1996;90(2):69-77. [https://doi.org/10.1016/S0954-6111\(96\)90201-2](https://doi.org/10.1016/S0954-6111(96)90201-2)
- Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2006;(2):CD000052. <https://doi.org/10.1002/14651858.CD000052.pub2>
- Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: A systematic review with meta-analysis. *J Pediatr* 2004;145(2):172-177. <https://doi.org/10.1016/j.jpeds.2004.04.007>
- Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2013;(9):CD000052. <https://doi.org/10.1002/14651858.CD000052.pub3>
- Fink JB. Aerosol device selection: Evidence to practice. *Respir Care* 2000;45(7):874-885.
- Dhand R. Aerosol therapy for asthma. *Curr Opin Pulm Med* 2000;6(1):59-70. <https://doi.org/10.1097/00063198-200001000-00012>
- Amirav I, Newhouse MT, Mansour Y. Measurement of peak inspiratory flow with in-check dial device to simulate low-resistance (Diskus) and high-resistance (Turbohaler) dry powder inhalers in children with asthma. *Pediatr Pulmonol* 2005;39(5):447-451. <https://doi.org/10.1002/ppul.20180>
- Adams N, Bestall JM, Lasserson TJ, Jones PW. Inhaled fluticasone versus inhaled beclomethasone or inhaled budesonide for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(2):CD002310. <https://doi.org/10.1002/14651858.CD002310.pub2>
- Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev* 2005;(1):CD002738. <https://doi.org/10.1002/14651858.CD002738.pub2>
- Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: A systematic review of the literature. *J Allergy Clin Immunol* 1997;100(4):452-457. [https://doi.org/10.1016/S0091-6749\(97\)70134-9](https://doi.org/10.1016/S0091-6749(97)70134-9)
- O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164(8):1392-1397. <https://doi.org/10.1164/ajrccm.164.8.2104102>
- Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. *Lancet* 2003;361(9363):1071-1076. [https://doi.org/10.1016/S0140-6736\(03\)12891-7](https://doi.org/10.1016/S0140-6736(03)12891-7)
- Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343(5):332-336. <https://doi.org/10.1056/NEJM200008033430504>
- Ducharme FM. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: Systematic review of current evidence. *BMJ* 2003;326(7390):621. <https://doi.org/10.1136/bmj.326.7390.621>
- Knorr B, Franchi LM, Bisgaard H, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):e48. <https://doi.org/10.1542/peds.108.3.e48>
- Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004;20(10):1549-1558. <https://doi.org/10.1185/030079904X3348>
- Valovirta E, Boza ML, Robertson CF, et al. Intermittent or daily montelukast versus placebo for episodic asthma in children. *Ann Allergy Asthma Immunol* 2011;106(6):518-526. <https://doi.org/10.1016/j.anai.2011.01.017>
- Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. *Clin Exp Allergy* 2001;31(4):616-624. <https://doi.org/10.1046/j.1365-2222.2001.01088.x>
- Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long-acting beta<sub>2</sub>-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naïve adults and children. *Cochrane Database Syst Rev* 2009;(4):CD005307. <https://doi.org/10.1002/14651858.CD005307.pub2>
- Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF, and the Dutch Asthma Study Group. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1998;158(1):213-219. <https://doi.org/10.1164/ajrccm.158.1.9706048>
- Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta<sub>2</sub>-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database Syst Rev* 2010;(4):CD005533. <https://doi.org/10.1002/14651858.CD005533.pub2>
- Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013;(12):CD009019. <https://doi.org/10.1002/14651858.CD009019.pub2>
- Bateman ED, Harrison TW, Quirce S, et al. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. *Respir Res* 2011;12:38. <https://doi.org/10.1186/1465-9921-12-38>
- Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013;(4):CD007313. <https://doi.org/10.1002/14651858.CD007313.pub3>
- Papi A, Corradi M, Pigeon-Francisco C, et al. Beclomethasone-formoterol as maintenance and reliever treatment in patients with asthma: A double-blind, randomised controlled trial. *Lancet Respir Med* 2013;(1):23-31. [https://doi.org/10.1016/S2213-2600\(13\)70017-2](https://doi.org/10.1016/S2213-2600(13)70017-2)
- Patel M, Pilcher J, Pritchard A, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: A randomised controlled trial. *Lancet Respir Med* 2013;(1):32-42. [https://doi.org/10.1016/S2213-2600\(13\)70007-9](https://doi.org/10.1016/S2213-2600(13)70007-9)
- Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;337(20):1412-1418. <https://doi.org/10.1056/NEJM199711133372002>
- Rodrigo GJ, Castro-Rodriguez JA. What is the role of tiotropium in asthma?: A systematic review with meta-analysis. *Chest* 2015;147(2):388-396. <https://doi.org/10.1378/chest.14-1698>
- Lofdahl CG, Reiss TF, Leff JA, et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ* 1999;319(7202):87-90. <https://doi.org/10.1136/bmj.319.7202.87>
- Price DB, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58(3):211-216. <https://doi.org/10.1136/thorax.58.3.211>
- Tamaoki J, Kondo M, Sakai N, et al., and the Tokyo Joshi-Idai Asthma Research Group. Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. *Am J Respir Crit Care Med* 1997;155(4):1235-1240. <https://doi.org/10.1164/ajrccm.155.4.9105060>
- Virchow JC, Jr, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. *Am J Respir Crit Care Med* 2000;162(2):578-585. <https://doi.org/10.1164/ajrccm.162.2.990504138>
- Sorkness CA, Lemanske RF, Jr, Mauger DT, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;119(1):64-72. <https://doi.org/10.1016/j.jaci.2006.09.042>
- Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: An evidence-based approach. *Med J Aust* 2003;178(5):223-225.
- Brozek JL, Kraft M, Krishnan JA, et al. Long-acting beta<sub>2</sub>-agonist step-off in patients with controlled asthma. *Arch Intern Med* 2012;172(18):1365-1375. <https://doi.org/10.1001/archinternmed.2012.3250>
- Hagan JB, Samant SA, Volcheck GW, et al. The risk of asthma exacerbation after reducing inhaled corticosteroids: A systematic review and meta-analysis of randomized controlled trials. *Allergy* 2014;69(4):510-516. <https://doi.org/10.1111/all.12368>

Accepted 7 May 2018.

## Appendix A. The SA Childhood Asthma Working Group (SACAWG)

**Epidemiology:** H Zar (leader), Western Cape; C Gray, Western Cape.

**Diagnosis of asthma:** R Masekela (leader), KwaZulu-Natal; S M Risenga, Limpopo; O P Kitchin, Gauteng; P Goussard, Western Cape.

**Assessment of asthma control:** R J Green (leader), Gauteng; A van Niekerk, Gauteng; D White, Gauteng; G Davis, Gauteng.

**Pharmacotherapy:** F E Kritzing (leader), Western Cape; A Jeevanathrum, Gauteng; P de Waal, Free State; S Kling, Western Cape; A Vanker, Western Cape; T C Gray, Western Cape; J Morrison, Western Cape; A Puterman, Western Cape; E Zöllner, Western Cape; D Rhode, Western Cape.

**Pharmacotherapy – other therapies:** A I Manjra (leader), KwaZulu-Natal; P M Jeena, KwaZulu-Natal; V Naidoo, KwaZulu-Natal; M Annamalai, KwaZulu-Natal; A van Niekerk, Gauteng.

**Self-management plans:** M Levin (leader), Western Cape; S Emanuel, Western Cape; D Hawarden, Western Cape; H Katz, Gauteng.

## Appendix B. Level of evidence

IA Evidence from meta-analysis and randomised controlled trials

IB Evidence from at least one randomised controlled trial

IIA Evidence from at least one controlled trial without randomisation

IIB Evidence from at least one or other quasi-experimental study

III Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-controlled studies

IV Evidence from expert committee reports, opinions or clinical experience of respected authorities

**Appendix B. Grades of Recommendation Assessment, Development and Evaluation (GRADE)**

<b>Level of recommendation</b>	<b>Quality of evidence</b>	<b>Definition</b>
A	High	High-quality research very unlikely to change our confidence in the estimate effect based on level I evidence
B	Moderate	Moderate-quality evidence, where future research is likely to have an important impact on our confidence in the estimate effect. Based on level II evidence or extrapolated from recommendations from level I evidence
C	Low	Low-quality evidence, where future research is likely to have an important impact on our confidence in the estimate effect. Based on level III evidence or recommendations from level I and II evidence
D	Very low	Very-low-quality evidence, where the estimate effect is uncertain. Based on level IV evidence or recommendations from level I, II and III evidence