Asthma treatment in children: A pragmatic approach

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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.

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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,[1] 2000[2] and 2009.[3] 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.[3] 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_1)) 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$_2$-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$_2$-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)†	200
Budesonide (nebulised)†	500
Fluticasone propionate (HFA)	100

ICS = inhaled corticosteroid; HFA = hydrofluoroalkane; pMDI = pressurised metered-dose inhaler.
*Adapted from Global Initiative for Asthma.[4]
†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†	100 - 200	200 - 500	>500
Mometasone furoate	110	220 - <440	≥440
	Adolescents (≥12 years old)		
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†	100 - 250	>250 - 500	>500
Fluticasone furoate‡	-	-	-
Mometasone furoate	110 - 220	>220 - 440	>440

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane.
*Ciclesonide is registered for children ≥12 years old.
† May be used at half the dose of budesonide equivalent.
‡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
		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.
*Adapted from Global Initiative for Asthma[4] and Hossny *et al.*[5]
†Indicated only for children ≥12 years old.

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†
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.
†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.

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.[5] A pMDI with holding chamber (spacer) is preferable to nebulised therapy owing to convenience, more effective lung deposition, fewer side-effects and lower cost.[6-8] 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. 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.[8,9] 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.[10,11] 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.[11,12] 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.[12] 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$_2$-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$_2$-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$_2$-agonist; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist.

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

- 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).[13-15] 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).[13,17,18]

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).[19-23]

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).[24]

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.[25,26] 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).[24-26] 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).[27] 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[40]	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[41]	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[40]	I
		Reduce maintenance ICS/formoterol dose to once daily and continue as needed with low-dose ICS/formoterol reliever	III
	Moderate- or high-dose ICS	Reduce ICS dose by 50%[41]	I
Step 2	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$_2$-agonist; LTRA = leukotriene receptor antagonist.
*Adapted from South African Childhood Asthma Working Group.[1]

dose of ICS and a reduced exacerbation rate requiring oral steroids or hospitalisation in the former group (evidence level I).[27-31] 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).[32]

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).[33] Similarly, the addition of an LTRA[34-37] (evidence level II) or slow-release theophylline[70] (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).[38,39] 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.

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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 Kritzinger (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)

Level of recommendation	Quality of evidence	Definition
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