



## GUIDELINE

## Guideline for the management of chronic asthma in children – 2009 update

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*Objective.* To revise the guideline for the diagnosis and management of chronic asthma in children in view of the following considerations: the existing South African Childhood Asthma Working Group (SACAWG) guideline was produced 10 years ago; diagnosis of asthma in young children remains a challenge; evidence-based treatment is the new paradigm; new treatment approaches to achieving and maintaining control; therapeutic roles of several medications have evolved; more studies and data on treatment in young children; new medications and formulations; a change of emphasis in assessing asthma control to guide treatment changes. The main aim of the guideline is to promote a better standard of treatment based on understanding of the pathophysiology and pharmacotherapy of asthma, and encouraging uniformity in asthma management.

*Evidence.* A detailed literature review by a working group of clinicians from relevant disciplines. The strategies recommended are classified according to the evidence category in Appendix B, and denoted as Evidence A, B, C and D.

*Recommendations.* These include an appropriate diagnostic approach, environmental control measures, treatment options, definition of asthma control, and strategies to achieve control.

*Endorsement.* The guideline document was endorsed by the South African Thoracic Society (SATS), the National Asthma Education Programme (NAEP), the South African Paediatric Association (SAPA) and the South African Academy of Family Practice.

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### 1. Background

The South African Childhood Asthma Working Group (SACAWG), a sub-committee of the Allergy Society of South Africa (ALLSA), first published its guideline for the management of chronic asthma in children and adolescents in 1992.<sup>1</sup> The guideline was revised in 1994<sup>2</sup> and 2000.<sup>3</sup> In the past decade, there have been significant advances in the management of asthma; these include treatment based on level of control, newer treatment options, new formulations of inhaled corticosteroids, and availability of low-cost spacers for delivering inhaled drugs.

The current revision was prompted by: (i) a need to expand the sections on diagnosis and treatment to include children  $\leq 5$  years old; (ii) the revised classification of asthma based on level of control; (iii) an ongoing need to emphasise the use of **controllers** (previously referred to as **preventers**) as the foundation of asthma treatment; and (iv) the positioning of newer treatment options for asthma (evidence-based approach), including combination treatment (inhaled

corticosteroid (ICS) plus a long-acting  $\beta_2$ -agonist (LABA)), leukotriene receptor antagonists, sublingual immunotherapy, omalizumab and macrolides.

The objectives of this guideline are to promote a better standard of treatment based on advances in the understanding of the pathophysiology and pharmacotherapy of asthma, and to encourage uniformity in the management of asthma.

### 2. Methodology

This 2009 asthma guideline update was undertaken after a meeting with a working group constituted by ALLSA. The working group is chaired by Professor Cas Motala.

The working group meetings were held in June 2008. Four task groups, each headed by a leader, were constituted: (i) Asthma diagnosis and assessment of level of control; (ii) Environmental control measures and immunotherapy; (iii) Pharmacotherapy: corticosteroids and steroid/LABA combinations; (iv) Pharmacotherapy: New treatments including leukotriene modifiers, anti-IgE and macrolides. The task groups were charged with reviewing the available scientific literature and assigning evidence levels according to the methodology utilized in current guideline documents: Categories A, B, C and D based on the strength of evidence levels (Appendix B). Subsequently, an editorial board, consisting of the chairperson and leaders of the task groups, was convened. The working group is aware of the trend toward application of GRADE<sup>4</sup>

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technology and will consider utilising this methodology in the future.

The working group met again in July 2009 to discuss the draft guideline document. Thereafter, the editorial board was tasked to finalise the document for publication. This project was sponsored by ALLSA.

### 3. Disease profile

Asthma is the most common chronic childhood disease, affecting 10 - 20% of South African children.<sup>5</sup> The burden of asthma affects the patients, their families, and general society in terms of lost work and school days, impaired quality of life, hospitalisations and mortality. Asthma typically begins in early life, and is often triggered by viral infections or environmental factors including allergens. Airway inflammation and airway hyper-responsiveness are the hallmarks of the disease. Characteristic symptoms include recurrent episodes of wheezing, breathlessness, chest tightness and coughing. In children  $\leq 5$  years, the clinical symptoms are variable and nonspecific. Furthermore, neither airflow limitation nor airway inflammation are possible to assess routinely in this age group. Diagnosing asthma in young children may therefore be difficult.

The goal of asthma treatment is to achieve control of the disease for prolonged periods with appropriate regard for the safety and cost of treatment required to achieve this. Defining satisfactory current clinical asthma control in children  $\leq 5$  years is problematic since it is almost exclusively dependent on reports from family/caregivers who may be unaware of or underreport the presence of asthma symptoms.

Recommendations in this guideline are based on currently available evidence. Health practitioners should strive to achieve the best possible therapy for each of their patients through motivation and education of parents and health care professionals, to ensure that all patients have access to appropriate medication.

### 4. Diagnosis

Asthma should be diagnosed in a child with chronic/recurrent wheeze with or without cough (owing to bronchoconstriction) triggered by multiple factors including viral infections, allergens, irritants (pollution), exercise and sudden emotional changes (e.g. crying, laughing) and which responds to an inhaled bronchodilator. Features supporting the diagnosis are a family or personal history of atopy, night cough, exercise-induced cough and/or wheeze and seasonal variation in symptoms. In children, allergy is often the main trigger that determines the severity of the disease. Early sensitisation, severe atopy and synergistic interaction between atopy and infections are risk factors for persistent asthma.<sup>6</sup> Cough variant asthma is a rare form of asthma which presents with cough but no wheeze and no evidence of airway obstruction on spirometry.<sup>7,8</sup>

#### 4.1 Children older than 5 years

A careful history and physical examination, together with objective evidence of reversible airflow obstruction after administration of a short-acting  $\beta_2$ -agonist (SABA) (an increase in forced expiratory volume in 1 second (FEV<sub>1</sub>) >12% or in peak expiratory flow rate (PEF) >15% after 10 minutes), will in most instances confirm the diagnosis. Monitoring symptoms and PEF using a diary card is also useful for making the diagnosis; diurnal PEF variability >20% is highly suggestive of asthma. Conditions that need to be considered when the diagnosis of asthma is uncertain are listed in Table I.

#### 4.2 Children 5 years and younger

The diagnosis of asthma in early childhood is challenging and has to be based largely on **clinical judgement** (assessment of symptoms and physical findings). Since the use of the label 'asthma' for wheezing in children has important clinical implications, it must be distinguished from other causes of persistent and recurrent wheeze (Table II).

Episodic wheezing and cough is very common even in children who do not have asthma, and particularly in those <3 years old. Three categories of wheezing have been described in children  $\leq 5$  years (retrospective epidemiological classification<sup>9</sup>): transient early wheezing, persistent early-onset wheezing, and late-onset wheezing. Despite this epidemiological classification, the diagnostic approach to these patients is poorly described, especially in low- and middle-income countries.

**Table I. Differential diagnosis of asthma in children older than 5 years**

Hyperventilation syndrome and panic attacks
Vocal cord dysfunction
Upper airway obstruction and inhaled foreign bodies
Other forms of obstructive lung disease (e.g. cystic fibrosis)
Non-respiratory causes of symptoms (e.g. left ventricular failure)

**Table II. Differential diagnosis of asthma in children 5 years and younger**

<b>Infections</b>
Post-viral wheezing
Tuberculosis (e.g. glandular compression of airways)
HIV disease (e.g. lymphocytic interstitial pneumonia)
<b>Congenital/perinatal problems</b>
Tracheomalacia
Cystic fibrosis
Chronic lung disease of the newborn
Congenital malformation causing narrowing of the intrathoracic airways
Primary ciliary dyskinesia syndrome
Immune deficiency
Congenital heart disease (e.g. L-R shunts)
<b>Mechanical problems</b>
Foreign body aspiration
Gastro-oesophageal reflux disease (GORD)

A simple clinical index (**asthma predictive index**) based on the presence of a wheeze before the age of 3, and the presence of 1 major risk factor (parental history of asthma or eczema) or 2 of 3 minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis), has been shown to predict the occurrence of asthma in later childhood in children in developed countries.<sup>10</sup> While useful to diagnose asthma in large epidemiological studies in Europe and America (Evidence B), this finding has not been applied in the context of African children, who have less atopy.

A recent publication categorised wheeze in young children into 2 broad groups: **episodic (viral) wheeze** and **multi-trigger wheeze**.<sup>11</sup> The group of children who have multi-trigger wheeze have symptoms precipitated by factors other than viral infections (such as allergens and exercise) and are likely to be asthmatic.

The diagnosis of preschool asthma should be based on a composite set of diagnostic criteria and, while no tests diagnose asthma with certainty in young children, the following may be considered as useful adjuncts in making a diagnostic decision:

#### 4.2.1 Clinical features

The categories of symptoms and therapeutic responses listed in Table III are highly suggestive of asthma (based on current evidence and clinical experience).

#### 4.2.2 Modified bronchodilator response test (MBR)<sup>12</sup> (Evidence D)

In this test, a patient suspected of having asthma (usually a young child with persistent or recurrent wheezing) is given a bronchodilator by nebuliser or metered-dose inhaler (MDI) with a spacer, and symptoms/signs are evaluated 10 - 15 minutes later. Asthmatics usually demonstrate a significant clinical response to a bronchodilator, as measured by reduction in wheeze or respiratory rate or improvement in air entry. Some children with viral-induced wheeze may also respond, so

the test forms part of an assessment for asthma and is not the sole criterion for diagnosis.

#### 4.2.3 Lung function testing

Lung function testing is useful for aiding the diagnosis of asthma in children >5 years. In general, they do not have a diagnostic role in younger children because of their inability to perform reproducible expiratory manoeuvres. Lung function testing for infants<sup>13</sup> and young children are only possible in specialised centres, and are mainly used for research purposes.

## 5. Goals and principles of management

### 5.1 Goals

The goal of asthma therapy is asthma control. Control implies that the asthmatic child is able to lead a normal and physically active life. The criteria for 'normal life' are to:

- be completely free from any symptoms, i.e. cough, wheeze and breathlessness
- attend school regularly and participate fully in all school activities, including sport
- sleep restfully, free from night-time cough and/or wheeze
- grow and develop normally
- minimise the number of attacks of acute asthma and avoid hospitalisation
- avoid or minimise medication-related side-effects.

### 5.2 Principles

A comprehensive therapeutic approach is required to meet the above objectives, which includes the following:

- early diagnosis and objective assessment of severity
- control of the environment to exclude cigarette smoke and reduce exposure to triggers such as viral infection and allergens
- optimal use of medications to limit side-effects and cost, using the most appropriate delivery system
- follow-up and regular re-evaluation (clinical evaluation and quality of life)
- patient and parent education.

## 6. Environmental control

Avoidance of allergens (based on history and allergy testing) and pollutants is recommended when there is a clear association between exposure and symptoms. Recommended avoidance measures are discussed below.

### 6.1 Indoors

#### 6.1.1 Tobacco smoke/other pollutants

Smoking should not be allowed in the home, and active steps should be taken to inform parents of the problem, encouraging

**Table III. Features suggestive of asthma in children <5 years**

#### Evidence A

Exercise-induced cough or wheeze  
Cough at night  
Symptoms persisting after the age of 3 years

#### Evidence B

Absence of seasonal variation  
Symptoms worsening with certain exposures  
Colds repeatedly going to the chest  
Response to a bronchodilator  
Response to a course of steroid  
Concomitant rhinitis, eczema or food allergies  
Family history of allergy or asthma

#### Evidence C

Wheezing more than 1 month

#### Evidence D

Modified bronchodilator response test

smokers to quit. Smoking during pregnancy should be strongly discouraged as the evidence indicates that *in utero* exposure to tobacco smoke is associated with a higher risk of developing wheezing early in life.

Other sources of biomass fuel exposure, such as open fires for cooking or heating, may trigger asthma or cause more severe asthma. Fluted chimneys and good ventilation in homes should be encouraged. Children should be kept away from open flames or fumes, e.g. a mother should avoid putting her baby on her back while cooking over open flames.

### 6.1.2 Indoor allergens<sup>14</sup>

A detailed history should identify which allergens are likely to be triggers of asthma symptoms. If there is uncertainty after taking a history, and the child has persistent asthma, then specific allergen testing by skin prick test or specific immunoglobulin E (IgE) is indicated. There is no evidence to support avoidance of allergens for primary prevention of asthma.

- **House dust mites.** Mattress, pillow and duvet covers with mite-impermeable characteristics are recommended, but mites will accumulate on mattress covers if these are not regularly washed<sup>15</sup> (Evidence B). Bedding should be washed regularly at temperatures >60°C. Rooms should be well ventilated. Where possible, carpets should be removed from the living areas and especially the bedrooms. Acaricides are ineffective. Other sources of house dust mites should also be considered, e.g. fluffy toys and feather pillows.
- **Cockroaches.** Cockroach allergy is widespread in South Africa. Cockroaches may be a cause of ongoing airway inflammation, and sensitivity to cockroaches is a risk factor for more severe asthma. Obsessive cleaning, bait stations and boric acid indoors can reduce cockroach numbers<sup>16</sup> (Evidence B).
- **Pets.** Asthmatics known to be allergic to dogs or cats should avoid contact with them. Cat allergens are notoriously difficult to eliminate and may persist for several months after the cat has been removed from the home. Use of a dust cloth is three times more effective in reducing allergen levels than vacuuming with a brush attachment<sup>17</sup> (Evidence B).
- **Mould.** Obvious sources of indoor mould in bathrooms, kitchens and damp areas of the home should be dealt with by proper plumbing, damp-proofing, mould-repellent paint and sodium hydroxide sprays. Products containing hypochlorite are effective in cleaning homes, achieving a low reduction in fungi, and improving quality of life – which was statistically significantly better than in a control group<sup>18</sup> (Evidence B).

## 6.2 Outdoors

### 6.2.1 Outdoor allergens

Moulds are important sources of outdoor allergens, and sensitive children are advised to avoid exposure to mouldy

places, e.g. farms, forests, compost heaps and parks, particularly in autumn, winter and spring. Grass pollens may be implicated in perennial asthma because of the particularly long grass season in South Africa.

## 7. Treatment

Pharmacotherapy is the cornerstone of asthma management, with appropriate medication and delivery devices to meet patients' needs and circumstances. When asthma is **first** diagnosed, it is convenient for initiation of treatment to classify it as **mild intermittent** or **chronic persistent** asthma that is **mild, moderate or severe** (Table IV).<sup>3</sup> However, the severity of asthma is variable, does not predict response to treatment, and is of little value in patients already on treatment. Periodic assessment of asthma control (Table V)<sup>19</sup> ([www.ginasthma.com](http://www.ginasthma.com)) and review of management are more relevant. Asthma severity assessment is used to initiate therapy, while asthma control is determined to monitor and adjust therapy.

### 7.1 Assessment of severity to initiate therapy

The method of assessment presented conforms to international assessment criteria. The following points should be noted:

- The assessment of severity is used to assign a child to a particular treatment group only as a starting point.
- The assessment of severity refers to a child's symptoms and lung function (PEF or FEV<sub>1</sub>) between acute episodes in a patient who is not receiving long-term therapy. Severity can also be measured, once asthma control is achieved, by the step of care (i.e. the amount of medication) required to maintain control.
- One or more features must be present to assign a grade of severity; a patient must be assigned to the most severe grade in which any feature occurs.
- In practice, about 70% of childhood asthmatics will fall into the **mild persistent** category, 25% into the **moderate persistent** group, and 5% into the **severe persistent** category.

### 7.2 Assessment of asthma control

Control refers to the degree to which the manifestations of asthma are minimised by therapeutic intervention and the goals of therapy are met. After therapy is initiated, the emphasis for clinical management changes to the assessment of asthma control (Table V). The level of asthma control will guide decisions either to maintain or to adjust therapy, i.e. step up if necessary, or step down if possible. Asthma control may be assessed clinically (symptoms, physical findings, reliever use), and by measurement of lung function and fractional exhaled nitric oxide (FE<sub>NO</sub>) in certain situations.

#### 7.2.1 Clinical assessment

Clinical assessment includes the frequency of daytime and nocturnal symptoms, the extent of limitation of activities, and

**Table IV. Classification of asthma severity based on symptoms and PEF in patients presenting for the first time on no treatment**

	Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Symptoms	≤2 days/week	<2 days/week but not daily	Daily symptoms	Continual symptoms
Night-time symptoms	≤2 incidents/month	3 - 4 incidents/month	>1 incident/week but not nightly	Frequent
PEF (predicted)	≥80% predicted	≥80% predicted	>60 - ≤80%	≤60%
PEF variability	<20%	20 - 30%	>30%	>30%

the need for reliever treatment (Tables V and VI). Patient-centred questionnaires such as the Childhood Asthma Control Test (cACT) are very useful for identifying children who are uncontrolled.<sup>20</sup> The cACT has been promoted for the assessment of asthma control in children ≥4 years old. The cACT has 7 questions regarding asthma symptoms present in the previous 4 weeks. The first 4 questions are completed by the child, while the last 3 are completed by the parent. A score of 20 or more is judged to be well-controlled asthma.

### 7.2.2 Spirometry

Spirometry (flow-volume loop) can only be performed reliably in children >5 years old. The most commonly used parameters derived from the volume/time plot are FEV<sub>1</sub> and the forced vital capacity (FVC). The most commonly used parameters derived from the flow/volume plot are PEF and the maximum mid-expiratory flow rate (MMEF). FEV<sub>1</sub> and PEF are utilised most frequently for assessing asthma control.

Spirometry should be performed:

- at the initial assessment
- after treatment is initiated and symptoms and PEF have stabilised
- during periods of progressive or prolonged loss of asthma control
- at least every 1 - 2 years, more frequently depending on response to therapy

Low FEV<sub>1</sub> indicates current obstruction and is a useful measure of risk for exacerbations, although it must be

**Table VI. Routine asthma follow-up questions**

1. How often have you had asthma symptoms in the last week?
2. How often in the last week have you woken at night because of asthma symptoms?
3. How often in the last week have asthma symptoms limited your ability to be active?
4. How many puffs of reliever medicine have you used in the last week?
5. Have you missed any days of school/work in the last month because of asthma?

emphasised that even children who have normal lung function experience exacerbations. PEF can be read directly off the flow-volume loop or it can be measured with a peak flow meter which can easily be used at home to monitor lung function. PEF has limitations in that it is effort-dependent; PEF changes do not always reflect changes in lung function, and are generally a late indicator of loss of asthma control. Among patients with mild intermittent or mild persistent asthma, PEF monitoring has no advantage over symptom monitoring.<sup>21</sup> Short-term daily PEF monitoring, however, should be considered for patients who have moderate to severe persistent asthma or a history of severe exacerbations (it may be helpful for assessing the severity of obstruction and evaluating response to bronchodilator therapy) and for patients who poorly perceive airway obstruction or worsening asthma.

### 7.2.3 Exhaled nitric oxide (FE<sub>NO</sub>)

FE<sub>NO</sub> is not a routine test of asthma control. For most children, monitoring of exhaled NO offers no benefit over

**Table V. Levels of asthma control (Global Initiative for Asthma (GINA) 2007)<sup>19</sup>**

Characteristics	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled (≥3 features of partly controlled asthma in any week)
Daytime symptoms: wheezing, cough, difficult breathing	<2/week	>2/week	>2/week
Limitation of activities	None	Any	Any
Nocturnal symptoms/awakening	None	Any	Any
Need for reliever/rescue treatment	<2/week	>2/week	>2/week
Lung function* (PEF/FEV <sub>1</sub> ) predicted or personal best (if known)	Normal	<80%	<80%

\* Applicable to children >5 years old.



clinical monitoring. It may, however, have value in certain circumstances such as a child with difficult-to-control asthma. FE<sub>NO</sub> values have been shown to increase before the onset of symptoms or loss of control and monitoring may, therefore, be used to predict loss of control.<sup>22</sup> It may also be useful for assessing compliance with anti-inflammatory therapy.

### 7.3 Principles of medication

When selecting medication for an asthmatic patient, the following principles apply:

- regular anti-inflammatory medication is indicated for persistent asthma
- inhaled therapy is preferable
- drugs are classified as:
  - relievers – short-acting bronchodilators with rapid onset of action that provide acute relief of symptoms
  - controllers – drugs with anti-inflammatory and/or a sustained bronchodilator action.

### 7.4 Route of administration

Inhaled therapy is the cornerstone of asthma treatment for all children. Most children can be taught to use inhaled therapy effectively. Considerations in choosing an inhaler device include the efficacy of drug delivery, cost, safety, ease of use, convenience and efficacy in a specific age group.<sup>23,24</sup> A metered dose inhaler (MDI) with spacer is preferable to nebulised therapy because of convenience, more effective lung deposition, fewer side-effects and lower cost.<sup>25,26</sup>

Spacers retain large drug particles that would be deposited in the oropharynx, so reducing oropharyngeal side-effects and systemic absorption and availability of inhaled drug. This consideration is especially important for ICS with poor first-pass metabolism such as beclomethasone dipropionate (BDP) and budesonide. Commercially produced spacers with well-characterised drug output characteristics, or a homemade spacer device made from a 500 ml plastic cold-drink bottle, are preferable.<sup>27</sup> A child's inhalation technique should be observed, and corrected if necessary, at the health-care consultation.

An MDI with a spacer is as effective as, or more effective than, nebulised treatment for of acute, severe asthma exacerbations.<sup>25,26</sup> Nebulisers have imprecise dosing, are expensive, waste large amounts of drug into the surrounding air, are time-consuming to use and care for, and require maintenance. They are mainly reserved for children who cannot use other inhalation devices. In general, nebulisers should be discouraged for home use and rather utilised in settings where oxygen administration is necessary and available. A general inhaler strategy for children is given in Table VII.

**Table VII. Choice of inhaler device for children**

Age group	Preferred device
Younger than 4 years	Pressurised metered-dose inhaler <b>plus</b> spacer with face mask
4 - 6 years	Pressurised metered-dose inhaler <b>plus</b> spacer with mouthpiece
Older than 6 years	Pressurised metered-dose inhaler with spacer and mouthpiece, or dry powder inhaler (DPI), or breath-actuated pressurised metered-dose inhaler

### 7.5 Relievers

These include SABAs (Evidence A) and anticholinergics. Short-acting xanthines are not recommended in the maintenance treatment of asthma.

#### 7.5.1 Short-acting $\beta_2$ -agonists

SABAs are generally used on an as-needed basis. Their use can be minimised by the optimal use of anti-inflammatory agents and controllers. SABA inhalers provide relief from acute symptoms of asthma.

#### 7.5.2 Anticholinergics (ipratropium bromide)

These drugs work by inhibiting vagally mediated bronchoconstriction. They are less potent bronchodilators than inhaled  $\beta_2$ -agonists and in general have a slower onset of action (30 - 60 minutes to maximum effect). They may be used in patients who cannot tolerate  $\beta_2$ -agonists or as adjunctive bronchodilator treatment in patients who do not obtain adequate symptom relief during acute asthma. There is no evidence for the long-term use of ipratropium bromide in the management of asthma.

### 7.6 Controllers

Controller therapy is recommended for all patients with persistent asthma. ICSs are the most effective controller therapy for asthma (Evidence A). LABAs have prolonged bronchodilatory action, but have weak anti-inflammatory (controller) effects. Leukotriene receptor antagonists (LTRAs) also have anti-inflammatory effects via different pathways to ICSs. Sustained-release (SR) theophyllines have also been shown to have weak anti-inflammatory effects at doses lower than those required for bronchodilatation.

#### 7.6.1 Inhaled corticosteroids (ICSs)

ICSs are the most effective medication for controlling symptoms, reducing the number of asthma-related hospitalisations, improving lung function, reducing the frequency of exacerbations, improving quality of life and reducing bronchial hyper-responsiveness<sup>19,28-34</sup> (Evidence A).

Inhaled therapy via an MDI with spacer is preferable to nebulised therapy because of the convenience, more effective

lung deposition, fewer side-effects and lower cost (Evidence A). For children >5 years old, a dry powder inhaler (DPI) or breath-actuated pressurised MDI may be alternatives to an MDI with spacer.

A number of different ICS preparations are available (Table VIII). Most ICSs should be given twice daily, but budesonide and ciclesonide are approved for use once daily in children with mild asthma. The most important determinant of appropriate dosing is the patient's response to therapy. ICS dose should be adjusted according to the level of control attained. Once control of asthma is achieved, the dose of medication should be carefully titrated to the **minimum** dose required to maintain control, thus reducing the potential for adverse effects.

### Side-effects

Most studies evaluating the systemic effects of ICS suggest that clinically effective doses of ICS are safe and the potential risks are well balanced by the clinical benefits<sup>19,33,34</sup> (Evidence A). However, studies using higher doses have been associated with detectable systemic effects on both growth and the hypothalamo-pituitary axis (HPA). Although there are fewer studies in children <5 years, the available data are similar to those from older children.<sup>19,34,35</sup> Generally, low doses of ICS have not been associated with any clinically important adverse systemic effects in clinical trials, and long-term use is considered safe.<sup>19,34-36</sup> Local side-effects, such as hoarseness and candidiasis, are rare in children when a spacer is used.

### Children older than 5 years

Most children are controlled on low daily doses of ICS (100 - 200 µg budesonide or equivalent (Table VIII). Some children require higher doses (400 µg/day) for control and for protection against exercise-induced symptoms. Clinical improvement occurs rapidly within 1 - 2 weeks, although maximum improvement may occur only after many weeks. Symptoms may recur after stopping ICS, with control deteriorating within weeks.

### Children younger than 5 years

Several studies of ICS in young children with asthma have shown similar clinical effects as in older children, including increases in lung function and number of symptom-free days, reduction in symptoms, need for additional medication,

caregiver burden, systemic glucocorticosteroid use, and exacerbations.<sup>30-32,34-36</sup> A systematic review of randomised double-blind controlled trials of ICSs in preschool children with wheeze showed statistically significant improvements in symptoms, exacerbation rates, lung function and airway hyper-responsiveness.<sup>31</sup> Of note is that exacerbations were reduced by almost 40%.<sup>31</sup> However, the dose-response relationships have been less well studied. Use of ICSs for up to 2 years has not been shown to induce remission of asthma; symptoms usually return when treatment is stopped.<sup>30</sup>

The clinical benefits of ICS for episodic, viral-induced wheeze are controversial. Systematic reviews found that episodic high-dose ICSs provide some benefit, reducing the need for oral corticosteroids by 50%; however, no effect on hospitalisation rates or duration of symptoms was found. Maintenance treatment with 400 µg/day of budesonide equivalent does not reduce the number or severity of wheezing episodes in episodic, viral-induced wheeze.<sup>37,38</sup>

Intermittent use of ICSs in preschool children with episodic viral wheeze at the time of symptoms does not reduce the risk of persistent wheeze at the age of 6 years, and symptoms return when steroid therapy is discontinued.<sup>39</sup> Therefore, the use of intermittent ICS for episodic wheeze cannot be recommended.

### Children younger than 2 years

There is a paucity of data on the efficacy and safety of ICS in children <2 years old.<sup>34-36</sup> In addition, wheezing caused by viral infections is very common in this age group but often resolves spontaneously or remits with age. In general, ICSs should only be used if symptoms are particularly troublesome and there is a clear response to treatment. As for older children, ICSs should be stepped down as control is achieved, so that the lowest ICS dose for control of symptoms is used.

## 7.6.2 Long-acting inhaled β<sub>2</sub>-agonists (LABAs)

### Children older than 5 years

A Cochrane review of 25 trials of 5 572 children reported that addition of LABAs did not significantly reduce the risk of asthma exacerbations requiring rescue systemic steroids, hospitalisation or duration of symptoms, but improved lung function compared with ongoing treatment with a similar dose of inhaled corticosteroids.<sup>40</sup> There was no evidence of

**Table VIII. Estimated equipotent daily dosage of ICS for children**

Drug	Low daily dose (µg)	Medium daily dose (µg)	High daily dose (µg)
Beclomethasone dipropionate	100 - 200	200 - 400	>400
Budesonide*	100 - 200	200 - 400	>400
Ciclesonide *	80 - 160	160 - 320	>320
Fluticasone	100 - 200	200 - 500	>500

\*Approved for once-daily dosing in patients with mild asthma.

As CFC preparations are taken off the market, medication inserts for HFA preparations should be carefully reviewed for the equivalent correct dosage.

increased serious side-effects or withdrawals with the addition of LABAs.

The effect of LABAs added to ICSs (7 studies, 1 021 children) compared with a higher dose of ICS also reported no difference in the incidence of asthma exacerbations requiring oral steroids or in the rate of hospitalisation for asthma. However, lung function was significantly improved in children on LABAs.<sup>40</sup> Studies have reported improvements in peak flow and lung function with the addition of a LABA.<sup>43-47</sup> However, the effect on symptoms, need for rescue medication and frequency of exacerbations have been less consistent.<sup>41,42</sup> The available paediatric studies suggest a modest improvement in lung function in children in whom LABAs are added to an ICS.<sup>40-47</sup>

LABAs are therefore currently positioned for maintenance treatment of children with asthma **only in combination with inhaled corticosteroids**. Combination products (i.e. those containing an inhaled corticosteroid and a LABA in the **same device**) are preferable to administration via separate inhalers. Fixed combination inhalers ensure that the LABA is always accompanied by an ICS. Combination products available in South Africa are shown in Table IX.

#### Side-effects

LABAs are generally well tolerated in children. Side-effects are similar in type and frequency to those of SABAs, and include muscle tremor, headache and palpitations. An increased risk of severe asthma exacerbations and mortality has been reported, particularly when used as monotherapy; therefore, LABAs should never be used without an ICS.<sup>19,41,42</sup>

#### Children younger than 5 years

The effect of LABAs or combination products has not been adequately studied in children ≤5 years old. There are no published double-blind randomised placebo-controlled trials on the addition of LABAs to ICSs in this age group. LABAs are currently approved for use in South Africa in children >4 years old. Therefore, **LABAs cannot be recommended at present for children <4 years old**.

#### 7.6.3 Leukotriene receptor antagonists/leukotriene modifiers

Leukotriene receptor antagonists (LTRAs) are an accepted treatment option for childhood asthma. They have a rapid

onset of action (within 1 - 3 hours),<sup>48</sup> are administered orally, treat asthma via a different pathway to other currently available medications (specific cysteinyl leukotriene receptor antagonists), and have been shown to be effective for aspirin-sensitive asthma.<sup>49</sup>

#### Side-effects

No significant safety concerns have been demonstrated for leukotriene modifiers in children. Headache and gastrointestinal upset are the most commonly encountered side-effects; skin rashes or flu-like symptoms are much less common.<sup>50,51</sup>

#### Children older than 5 years

LTRAs provide clinical benefit in children >5 years old at all levels of severity<sup>52-56</sup> (Evidence B), but generally less than those of low-dose ICSs.<sup>57</sup> Leukotriene modifiers provide partial protection against exercise-induced bronchoconstriction.<sup>56,57</sup> As add-on treatment in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers provide moderate clinical improvements, including a significant reduction in exacerbations<sup>52,58,59</sup> (Evidence B).

#### Children younger than 5 years

LTRAs are safe and effective for treatment of asthma in young children, from as early as 6 months of age.<sup>60-66</sup> LTRAs have been proposed as alternative first-line therapy to ICSs for episodic or mild persistent asthma<sup>67</sup> (Evidence D), particularly in children who have difficulty in utilising inhalation treatment, with poor compliance, or where exercise-induced bronchospasm (EIB) is a dominant component of asthma. To date, no studies have evaluated the role of LTRAs as add-on therapy to inhaled steroids in children ≤5 years old.

Asthma and allergic rhinitis are frequently co-morbid conditions (80%); however, both are often treated as separate entities. With the concept of the 'united airway' disease in which asthma and allergic rhinitis are regarded as manifestations of a single disorder, treating one disease may affect the control of the other. In certain countries (but not in South Africa), LTRAs are approved for treatment of both allergic rhinitis and asthma.<sup>68-70</sup>

#### 7.6.4 Theophylline

Theophylline has been used in the treatment of asthma mainly as a bronchodilator (10 - 20 mg/kg/day), though it may also have anti-inflammatory effects at lower doses (5 - 10 mg/kg/day).<sup>71-74</sup> However, the anti-inflammatory effects of theophylline are small (less than that of low-dose ICSs) and side-effects are common.<sup>75</sup> Theophylline may be used as alternative, adjunctive therapy with ICSs in children >5 years old (Evidence D).<sup>74</sup> Monitoring of serum theophylline concentration is essential. **Long-term treatment with theophylline is not generally recommended in young children because of its adverse effects.**

**Table IX. Combination products available in South Africa**

Combination	Device	Dose (µg)
Salmeterol/fluticasone	DPI (Accuhaler)	50/100
		50/250
		50/500
Salmeterol/fluticasone	MDI CFC-free	25/50
		25/125
		25/250
Formoterol/budesonide	DPI (Turbuhaler)	4.5/80
		4.5/160
		9/320



**Side-effects**

The most common side-effects of theophylline are anorexia, nausea, vomiting and headache. Mild central nervous stimulation, palpitations, tachycardia, arrhythmias, abdominal pain, diarrhoea and, rarely, gastric bleeding may also occur. These side-effects are mainly seen at doses >10 mg/kg/day. The risk of adverse effects is reduced if treatment is initiated with daily doses around 5 mg/kg/day and then gradually increased to 10 mg/kg/day. Severe overdosing with theophylline can be fatal.

**7.6.5 Oral corticosteroids**

Oral corticosteroids such as prednisone may be considered in patients with poorly controlled severe asthma on optimal doses of ICS and additional controller therapy (Evidence D).<sup>19,34,76</sup> Oral corticosteroids, while relatively inexpensive, are associated with serious **systemic side-effects** including growth suppression, obesity and adrenal suppression. Because of the side-effects of prolonged use of oral steroids, these agents should only be used for acute exacerbations, and then only for a maximum of 5 - 7 days at a dose of 1 - 2 mg/kg/dose of prednisone given once daily. It is not necessary to taper oral steroids if used as a short course. Maintenance treatment with daily or alternate-day oral steroids is indicated only in those patients not controlled with high-dose inhaled steroids and additional controller therapy. In children on oral steroids, increased dosage should be given during episodes of increased stress, e.g. surgery.

**8. Other treatment options****8.1 Immunotherapy**

The Expert Panel of the USA's Department of Health and Human Services<sup>76</sup> recommends that allergen immunotherapy be considered for patients who have persistent asthma if there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B).

A meta-analysis of 75 randomised placebo-controlled studies has confirmed the effectiveness of subcutaneous immunotherapy in asthma with a significant reduction in asthma symptoms and medication and with improvement in bronchial reactivity<sup>77</sup> (Evidence A).

Immunotherapy is also effective for children when used sublingually<sup>78</sup> (Evidence B). Sublingual immunotherapy is effective in paediatric patients with allergic rhinitis<sup>79</sup> (Evidence A) and has an effect on inflammatory parameters and bronchial hyper-reactivity in asthmatic children sensitised to house dust mites<sup>80</sup> (Evidence B). Although both subcutaneous and sublingual immunotherapy are effective in asthmatic children (monosensitive to house dust mite or pollen), the latter is safer (confirmed in post-marketing studies<sup>81</sup>) (Evidence B). Based on the above evidence, sublingual immunotherapy could be

used as adjunctive treatment to pharmacotherapy in children >5 years old with rhinitis and mild to moderate asthma (FEV<sub>1</sub> >80%), to enhance asthma control and, in some cases, effect a cure.

**8.2 Omalizumab**

Omalizumab (anti-IgE) is a monoclonal antibody that prevents binding of IgE to the high-affinity receptors on basophils and mast cells. Anti-IgE is used as adjunctive therapy for patients ≥12 years old with severe persistent asthma who have sensitivity to relevant inhalant allergens, e.g. house dust mite, cockroach, cat and dog. Isolated cases of anaphylaxis to anti-IgE have been reported in adults. Omalizumab is administered via subcutaneous injection every 2 - 4 weeks. The therapeutic index of this agent in children is still being defined. Clinicians who administer omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur. Anti-IgE should preferably be administered by a specialist. Mode of administration and cost could limit the use of this treatment, particularly in children.

**8.3 Macrolides**

Macrolide antibiotics have recognised anti-inflammatory properties in addition to their antimicrobial effects. Although some benefits have been reported in adults with chronic persistent asthma, a meta-analysis of 7 randomised controlled clinical trials involving both children and adult patients (N=416) with chronic asthma and treated with macrolides or placebo for >4 weeks, reported insufficient evidence to support their use in patients with chronic asthma.<sup>82</sup>

**8.4 Antihistamines**

Antihistamines have no proven benefit for asthma symptom control, but may be useful for control of symptoms of co-existing allergic diseases such as rhino-conjunctivitis, urticaria and atopic eczema.

**8.5 Unnecessary therapy**

The following are of no benefit in the treatment of childhood asthma: antibiotics, cough syrups, mucolytics, ionisers and breathing exercises. Complementary and alternative medications and interventions bear insufficient evidence to permit recommendations. Physiotherapy is indicated in children only where lobar collapse is documented.

**9. Self-management plan for asthma**

The responsibility for patient education rests with the doctor, and should be shared with trained health care professionals. Patients and parents must be encouraged to participate actively in their own management. In South Africa, the National Asthma Education Programme (NAEP) provides free access to patient educational materials as well as symptom/adherence

diaries and a self-management action plan. These are available at [www.asthma.co.za](http://www.asthma.co.za).

Patient education significantly improves asthma control and decreases hospitalisation rates (Evidence A).<sup>83</sup> The influence of education is greater in moderate-severe, compared with mild-moderate, asthma. Intensive education is of greater benefit than limited education, and written plans are superior to oral instructions. Education given at follow-up visits is more effective than education during emergency visits.<sup>84</sup> Culture-specific programmes for adults and children from minority groups with asthma are more effective than generic programmes in improving quality of life, asthma knowledge, asthma exacerbations and asthma control (Evidence B).<sup>85</sup>

Educational programmes should be considered a part of the routine care of all patients with asthma. Asthma self-management education should be integrated into all aspects of asthma care and reinforced at each follow-up visit. **The elements of a self-management plan** are summarised as follows:

- Avoid known allergens and nonspecific triggers, particularly tobacco smoke.
- Educate patients and parents about asthma and its treatment, e.g. difference between controller and reliever treatment, correct use of inhalers, use of a spacer where necessary, and correct use of peak flow meter where appropriate.
- Provide patients and parents with an asthma adherence and symptom diary as a tool for monitoring asthma control.
- Provide all patients with a written action plan that includes instructions for both daily management (long-term control medication, if appropriate, and environmental control measures) and actions to manage worsening asthma (what signs, symptoms and PEF measurements (if used) indicate worsening asthma; what medications to take in response; what signs and symptoms indicate the need for immediate medical care). Written action plans are particularly recommended for patients who have moderate or severe persistent asthma, or a history of severe exacerbations, or poorly controlled asthma.
- Arrange for a Medic-Alert badge for patients with severe steroid-dependent asthma, known drug hypersensitivity such as aspirin sensitivity, and brittle asthma.

## 10. Follow-up and review

Re-evaluate treatment within 2 - 6 weeks and adjust therapy as appropriate. The main objective of follow-up visits is to determine whether asthma is controlled or not (Table V). In addition, the following points should be assessed/monitored at each visit:

- inhaler technique
- adherence

- written action plan
- patient concerns
- side-effects of medication
- growth (weight, height).

## 11. Adjusting therapy based on control (Fig. 1)

If asthma is uncontrolled, treatment may be stepped up as follows:

- **For children younger than 5 years:** If asthma is not controlled on low-dose ICS, doubling the initial dose of ICS (medium-dose ICS) is the preferred controller option. Alternatively, consider adding a LTRA or LABA (LABA approved only in children >4 years old) to the ICS. If uncontrolled on medium-dose ICS and a LTRA (or LABA in children >4 years old), refer to a specialist for further evaluation and management.
- **For children older than 5 years:** Options for stepping up treatment include increasing the dose of ICS (medium dose) or adding a LABA or LTRA. If still uncontrolled, consider further increasing the ICS dosage or adding another controller therapy if already on medium doses of ICS.<sup>20</sup> If still uncontrolled, refer to a specialist.

The need for additional treatment should be re-evaluated at each visit and maintained for **as short a period as possible**.

**If asthma is well controlled for at least 3 months**, reduce treatment. There are few studies to guide step-down therapy. A suggested regimen for step-down treatment is: first discontinue oral steroids; next reduce the dosage of ICS (if on high dose); and thereafter discontinue additional controller treatment. The child should be maintained on the lowest effective dose of ICS. Assess control on a regular basis.

There are many factors in poor asthma control (Table X), including lack of adherence, incorrect inhaler technique, inadequate therapy for the degree of severity of asthma, environmental triggers, and presence of co-morbid conditions. Alternative causes of recurrent wheezing must also be sought. Before stepping up or changing treatment, these factors should be excluded.

**Table X. Reasons for poor asthma control (Evidence A)**

Lack of adherence to controller medication
Inability to use inhaler or powder device correctly
Inadequate drug dosage
Ongoing allergen exposures
Uncontrolled allergic rhinitis/sinusitis
Gastro-oesophageal reflux
Psychosocial problems (family dysfunction, behaviour problems, depression)
Use of medications with adverse events (e.g. $\beta$ -blockers, aspirin, NSAIDs)
Incorrect diagnosis

Level of control	Treatment action
Controlled	Maintain and find lowest controlling step
Partly controlled or uncontrolled	Step up until controlled

**Before stepping up treatment:**

- Check adherence
- Check inhaler technique
- Assess for co-morbid conditions
- Review diagnosis

**Controller treatment (Level 1)**

- **Low-dose inhaled corticosteroid (ICS) – any age**  
Alternative: Leukotriene receptor antagonist (LTRA)

Controlled  
Reduce treatment



Uncontrolled  
Increase treatment

**Controller treatment (Level 2)**

- **≤5 years: Medium-dose ICS**  
Alternative: Low-dose ICS plus LTRA
- **>5 years: Medium-dose ICS or low-dose ICS plus long-acting β<sub>2</sub>-agonist (LABA)\***  
Alternative: Low-dose ICS plus LTRA

Controlled  
Reduce treatment



Uncontrolled  
Increase treatment

**Controller treatment (Level 3)–Specialist care**

- **≤5 years: Medium-dose ICS plus LTRA**
- **>5 years: Medium-high dose ICS plus LABA\***  
Alternative: Medium-high dose ICS plus LTRA  
Consider adding oral steroids (alternate-day regimen) if asthma is poorly controlled on medium-high dose ICS plus another controller

**All patients**

- Asthma education
- Environmental control
- As-needed reliever

Preferred controller options are shown in grey-shaded areas  
\*LABA approved in children >4 years old, but must only be used in combination with ICS  
Sustained-release (SR) theophylline may be used as alternative adjunctive therapy with ICS in children >5 years old if other controllers unavailable

Fig. 1. Adjusting treatment of asthma based on control.

## 12. Non-adherence

Studies of adults and children have shown that approximately 50% of those on long-term therapy fail to take medications as directed at least part of the time.<sup>86</sup> **Non-adherence** may be defined in a non-judgemental way as failing to take treatment as agreed upon by the patient and the health care professional. Non-adherence may be identified by prescription monitoring, pill counting or drug assay, but at a clinical level it is best detected by asking about therapy in a way that acknowledges the likelihood of incomplete adherence (e.g. 'So that we may plan therapy, do you mind telling me how often you actually take the medicine?' or 'How many times in a normal week do you forget to take the medicine?'). Specific drug and non-drug factors involved in non-adherence are listed in Table XI.

**Strategies to promote adherence** include:

- prescribing a simple dosage regimen (once or twice daily) and as few drugs as possible
- selecting treatment that achieves outcomes and addresses preferences that are important to the patient, and reminding patients that adherence will help to achieve goals of treatment
- assessing the patient's and family's level of social support, and encourage family involvement
- tailoring the self-management approach to the needs and literacy levels of the patient, and maintaining sensitivity to cultural beliefs and ethno-cultural practices. Individualised self-management of asthma has been shown to improve medication adherence and asthma control.<sup>87</sup>

## 13. Co-morbid conditions

It is necessary to identify and treat co-morbid conditions, such as those below, that may affect asthma control. If these conditions are treated appropriately, asthma control may improve.

- **Rhinitis or sinusitis** symptoms or diagnosis should be evaluated in patients who have asthma, because of the interrelationship of the upper and lower airways. There

is sufficient evidence that co-existing allergic rhinitis or sinusitis may impair asthma control in adults.<sup>88</sup> In addition, therapy for allergic rhinitis or sinusitis has been shown to improve asthma control. Treatment of allergic rhinitis includes intranasal corticosteroids, antihistamine therapy, and, in selected cases, immunotherapy.<sup>89</sup> Treatment of sinusitis includes intranasal corticosteroids and antibiotics. Evidence is inconclusive regarding the effect of sinus surgery on asthma in patients with chronic rhinosinusitis.

- **Gastro-oesophageal reflux disease (GORD)** treatment may benefit patients who have asthma and complain of frequent heartburn, particularly those who have frequent nocturnal asthma symptoms. Even in the absence of suggestive GORD symptoms, consider evaluation for GORD in patients who have poorly controlled asthma.
- **Allergic bronchopulmonary aspergillosis** may be considered in patients who have asthma and a history of pulmonary infiltrates, have IgE sensitisation to *Aspergillus*, and/or are corticosteroid-dependent. Diagnostic criteria include a positive immediate skin test and elevated serum IgE and/or IgG to *Aspergillus* and central bronchiectasis.
- **Obese** patients who have asthma may be advised that weight loss, in addition to improving overall health, could also improve asthma control.
- **Stress and depression** that not well controlled should be considered in patients who have asthma. Additional education to improve self-management and coping skills may be helpful. Referral to a child psychiatrist/psychologist may be necessary.

## 14. Referral to a specialist

The majority of asthmatics can be managed optimally in a primary health care facility, provided that the elements of the asthma guideline are followed. Some patients may require referral to a specialist; this is recommended if the goals of management are not achieved, or for the following reasons:

- diagnosis is in doubt
- unstable asthma

**Table XI. Factors involved in non-adherence**

Drug factors	Non-drug factors
Difficulties with inhaler devices	Misunderstanding or lack of instruction
Awkward regimens (e.g. four times daily or multiple drugs)	Fears about side-effects
Side-effects	Dissatisfaction with health care professionals
Cost of medication	Unexpressed/undiscussed fears or concerns
Dislike of medication	Inappropriate expectations
	Poor supervision, training or follow-up
	Anger about condition or its treatment
	Underestimation of severity
	Cultural issues
	Stigmatisation
	Forgetfulness or complacency
	Attitudes toward ill health

- parents or general practitioners need further support
- child on a high dose of ICS (>400 µg beclomethasone equivalent per day)
- oral steroids are required regularly
- after a life-threatening episode
- frequent hospitalisations or visits to an emergency room
- if immunotherapy or omalizumab is considered.

## Disclaimer

This national clinical guideline is for reference and educational purposes only and is not intended to be a substitute for the advice of appropriate health care professionals or for independent research and judgement. Some of the medications mentioned in this guideline are used off-label but with the best evidence available.

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## Endorsement

This guideline has been endorsed by SATS, NAEP, SAPA and the South African Academy of Family Practice.

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## Appendix A: Members of SACAWG task groups (2008/9): chronic asthma

### Diagnosis of asthma/assessment of asthma control

<b>R J Green (leader)</b>	Gauteng
A Halkas	Gauteng
R Masekela	Gauteng
E A Moosa	Gauteng
S Ponde	Gauteng

### Environmental/immunotherapy control

<b>P C Potter (leader)</b>	Western Cape
A S Puterman	Western Cape
M Levin	Western Cape
D Hawarden	Western Cape
G Davis	Gauteng

### Pharmacotherapy: new steroids and steroid/LABA combinations

<b>H J Zar (leader)</b>	Western Cape
K Simmank	Gauteng
H Lewis	Gauteng
M J Mercer	Western Cape
S M Legodi	Gauteng
W Karshagen	Free State

### Pharmacotherapy: new treatments

<b>A I Manjra (leader)</b>	KwaZulu-Natal
M Davis	Gauteng
F Mokgoadi	Limpopo
M Ossip	Gauteng
O F Joona	KwaZulu-Natal
A van Niekerk	Gauteng

## Appendix B: Evidence grades and levels used in this guideline

Grade	Definition
<b>A</b>	Scientific evidence from randomised controlled trials (RCTs) in the target population, with statistically significant results that consistently support the guideline recommendations; supported by level 1 or 2.
<b>B</b>	Scientific evidence from well-designed, well-conducted observational studies in the target population, with statistically significant result consistently supporting the guideline recommendation; supported by level 3 or 4 evidence. Alternatively, extrapolated evidence from RCTs of populations (level 1 or 2) other than the target (paediatric) population.
<b>C</b>	Scientific evidence from laboratory studies, animal studies or case studies; supported by level 5 evidence.
<b>D</b>	Expert opinion providing the basis for the guideline recommendation. Scientific evidence either inconsistent or lacking.
Level	
<b>1</b>	Well-conducted and designed RCT
<b>2</b>	RCT with significant threats to validity
<b>3</b>	Observational study with a concurrent control group
<b>4</b>	Observational study with historical control
<b>5</b>	Bench study, animal study, or case series