

PRESCHOOL ASTHMA: KEY MESSAGES TO THE PAEDIATRIC REGISTRAR...

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ABSTRACT

Preschool asthma is now recognised as a separate entity from other phenotypes of preschool wheezing. South Africa has alarmingly high morbidity and mortality asthma rates, with the prevalence of asthma still rising. Identifying the preschool asthmatic can be challenging – it remains a diagnosis of exclusion and one based on clinical symptomatology. Healthcare practitioners should refrain from prescribing inhaled corticosteroids for prolonged periods, without the efficacy of it. Early (three months after starting treatment) follow-up is indicated to evaluate whether clinical improvement occurs and, if not, early discussion with a pulmonologist or allergist should occur. Well-defined asthma diagnosis and treatment regimes are now available in South Africa but we are not currently adhering to them. Under- and postgraduate students and registrars should familiarise themselves with these guidelines and apply them in daily practice. Asthma should *not* be treated with a short-acting bronchodilator alone. The majority of asthmatic children should improve with adequate inhaled corticosteroids and, if not, either the basic principles of asthma treatment are being overlooked or the child does not in fact have asthma!

INTRODUCTION

Asthma is the most common childhood lung condition. The International Study of Asthma and Allergies in Childhood (ISAAC) – the largest asthma-prevalence study ever – used questionnaires and self-reported symptoms of asthma (ie wheeze) to determine the global prevalence of asthma in 98 countries. ISAAC (Phase III) finished in 2002 and reported symptoms in children aged 6–7 years and 13–14 years to be 11.5% and 14.1% respectively. It should be noted that almost half of the children surveyed in South Africa had symptoms of uncontrolled asthma.¹ In the past few years, plateauing, even declining prevalence rates have been observed in high-income countries. Middle- and low-income countries such as South Africa still report a rising prevalence.²

The Global Asthma Network (2018) reports that South Africa has the third-highest asthma-related death rate in low- and middle-income countries worldwide for the period 2011 to 2015.³ This should be a worrisome statistic to all healthcare providers in South Africa.

So, where are we failing our patients? Are patients not using their asthma medication? Are we not teaching them how to use their inhalers correctly? Are many South African children still untreated because healthcare professionals are missing the diagnosis of asthma, or are patients not being referred for appropriate care? Are patients still being treated for asthma with a short-acting bronchodilator (SABA) alone (step 1), when in fact, they should be treated with an inhaled corticosteroid?

Preschool asthma has its own unique challenges regarding diagnosis and management. Clear, evidence-based guidelines

now exist for treating the preschool asthmatic and assessing asthma control. The reader is referred to the South African Childhood Asthma Working Group's (SACAWG) published guidelines, recently updated and brought into line with global recommendations.^{4–6} These guidelines should form part of the 'need-to-know' reading material of any paediatric registrar in training. This review article will not be a repetition of these guidelines, but will rather highlight some important and practical aspects of preschool asthma.

DEFINITION OF ASTHMA

Asthma is characterised by the limitation of variable expiratory airflow secondary to airway inflammation.⁷ Symptoms such as coughing, wheezing and shortness of breath mainly occur when forced expiratory airflow (FEV1) falls below a critical level (often at night, in the early morning or during physical activity). These symptoms may therefore vary diurnally, from day to day and from season to season. A history of acute onset of respiratory symptoms (often triggered by a respiratory airway infection, allergens/irritants, emotions or a change in weather pattern) should alert the clinician to the possibility of an asthma diagnosis. Often, asthmatics appear completely normal upon examination during consultation visits.

ASTHMA PHENOTYPES AND ENDOTYPES

Major advances have been made recently in identifying the different phenotypes and endotypes (distinct underlying pathophysiological, cellular and molecular pathways) of asthma. Ultimately, the aim is to adopt a targeted, personalised treatment strategy instead of a blanket, and 'one size fits most

or all' approach to treatment. Two different types of airway inflammation are described in asthmatics: Type 2 (eosinophilic asthma), which is subdivided in allergic eosinophilic and non-allergic eosinophilic. Non-type 2 (non-eosinophilic asthma) comprises neutrophilic and paucigranulocytic asthma.⁸ Less is known about this group in children.

The allergic asthma phenotype is often characterised by early-life skin-barrier dysfunction, with early identification of transcutaneous aeroallergen sensitisation. In a South African study that looked at children with moderate to severe atopic dermatitis (AD), 89% of children were sensitised to at least one aeroallergen (most commonly house-dust mite), 39% had symptoms of asthma and 53% had symptoms of allergic rhinitis (AR).⁹ T-helper type 2 lymphocytes and mast cells drive airway inflammation in an allergen-specific manner, producing demonstrable IgE-antibodies.¹⁰ In non-allergic eosinophilic asthma, innate lymphocytes such as natural killer T cells (NKT cells) and innate lymphoid type 2 (ILC2) cells contribute to airway eosinophilia via the production of interleukin 5 and in response to pollutants or infectious agents.^{11–15} The obese asthmatic is now recognised as a separate, distinct asthma phenotype. Obesity has been shown to be an independent risk factor for a decreased FEV1/FVC ratio in school-age children.¹⁶ Here, adipokines are the main inflammatory drivers.¹⁷

IS IT PRESCHOOL WHEEZING OR ASTHMA?

Wheezing (without underlying asthma) in preschool children is common. One-third of children will wheeze before their third birthday and roughly up to 25% of children will have had at least one wheezing episode before their sixth birthday.^{5,17,18} Viral bronchiolitis is transient and far more common than asthma in children under the age of two years – this diagnosis should be entertained first before the diagnosis of preschool asthma is made (see Figure 1).

The 2008 phenotypical classification proposed by the European Respiratory Society (ERS) distinguishes between children with distinct wheezy episodes during viral infections (episodic viral wheezing) and children with persistent wheezing, varying in degree of intensity and linked to environmental triggers (multi-

trigger wheezing). This classification is not very useful in daily practice, probably due to the fact that more than half of these patients can phenotypically 'switch' from one group to the other over a period as short as one year (see Figure 1).¹⁷ Obsessively trying to classify the wheeze and using terms such as 'evolving asthma' lead to unnecessary uncertainty, with a subsequent delay in the diagnosis and treatment of airway inflammation with inhaled corticosteroids.

PREDICTING ASTHMA IN THE PRESCHOOLER

AD is now recognised as one of the strongest predictors of asthma in childhood. Longitudinal prospective birth-cohort studies recognise early onset and severe AD, as well as AD persistence, parental atopy and filaggrin (FLG) mutations, as risk factors for AD advancement into other atopic disorders.⁴¹ The most recently studied Canadian Healthy Infant Longitudinal Development (CHILD) cohort identified AD as a risk factor for asthma at three years of age, only if it was accompanied by sensitisation to inhalants or foods, or both.⁴² In a South African study, up to 80% of children with moderate to severe AD had asthma and/or AR, and an increased severity of AD and co-morbid food allergy were associated with respiratory allergy.⁴⁰ A defective skin barrier should therefore be appreciated as an important entry point of food allergens and aeroallergens.³⁹ Therefore, protecting an infant's skin barrier (eg with early emollient application) to prevent AD makes a lot of sense as a primary prevention strategy for asthma.

The Asthma Predictive Index (API), developed initially from the Tucson birth cohort, uses parental history of asthma, frequency of wheezing episodes, wheezing with colds and the presence of eczema, AR and serum eosinophilia, to calculate a scored index. It is an attempt at predicting the likelihood of having asthma at the age of six years.¹⁹

The South African Childhood Asthma Working Group (SACAWG), in line with the GINA-guidelines, reiterates that findings from the Tucson cohort should not be generalised and applied globally, mainly because of differences in allergy and asthma prevalence in different population groups.^{5,20} Also, this index does not account for severity of wheezing episodes.

DIAGNOSIS OF ASTHMA

So, how do we diagnose asthma in preschool children? Currently, the answer to this question is simply this: a good history and a committed trial of inhaled corticosteroid treatment, administered correctly.¹⁷ The severity of asthma symptoms (hospital admissions requiring additional oxygen), personal atopic features or a first-degree relative with allergy (eg asthma, hay fever), frequency (>3 wheezy episodes per year), temporal pattern of symptoms with environmental exposure and reversibility of bronchoconstriction by administering SABA are all sensitive indicators of asthma.⁵

Remember: if there are distinct episodes of wheezing and/or coughing that respond to a bronchodilator, with normal episodes in between, this should be labelled as asthma and treated with an inhaled corticosteroid (a 'controller').

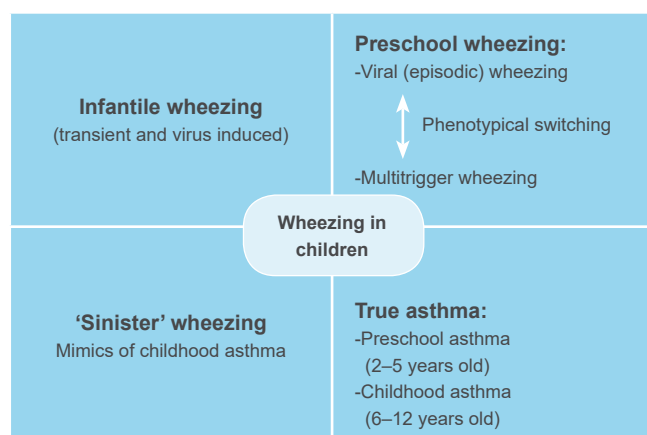


Figure 1: For practical purposes, it helps to classify wheezing in children into four major groups.

TABLE 1: SYMPTOMS OF PRESCHOOL ASTHMA

SUPPORTED BY LARGE RANDOMISED CONTROLLED TRIALS	SUPPORTED EVIDENCE IN SMALLER RANDOMISED CONTROLLED TRIALS	SUPPORTED EVIDENCE IN OBSERVATIONAL STUDIES AND EXPERT PANEL OPINION
Symptoms with physical activity/playing	Response to a bronchodilator (short-acting beta-agonist)	Wheezing continuously (for >1 month)
Nocturnal awakening due to troublesome symptoms	Seasonal variation in symptoms	A positive modified bronchodilator test (objectively reporting an improvement of respiratory symptoms after 20 minutes of salbutamol nebulisation) can be performed as an in-office test.
Symptoms persisting after three years of age	Viral colds repeatedly 'going to the chest'	
	Symptoms with specific exposures (including emotional upsets – for example, crying/laughing)	
	Symptoms improving after a short course of oral corticosteroids. (Avoid repeated and prolonged courses of oral steroids and start on an inhaled corticosteroid early to control symptoms)	
	Other signs of atopy present: AD, AR, food allergy	

Because asthma is often diagnosed by using only subjective symptoms, it might be over-diagnosed in daily practice.²¹ It should be emphasised that, at some point, an objective and documented proof of expiratory airflow reversibility is necessary to confirm the clinical suspicion of asthma – especially following a three-month 'trial' period of effectively administering inhaled corticosteroids – otherwise the diagnosis of asthma will remain presumptive.

The presence of important symptoms (summarised in Table 1) supports a diagnosis of asthma in the preschooler.^{5,20}

Remember: *not all asthmatics wheeze*. Predominantly, coughing without wheezing may also indicate asthma.

Asthma is objectively diagnosed by using specific pulmonary function test parameters. Performing pulmonary function tests in younger children may be technically difficult and often needs to be repeated more than once in order to confirm the diagnosis. The forced mid-expiratory flow (FEF_{25–75}) accurately reflects smaller airway obstruction and has been reported as a sensitive marker for asthma exacerbations, especially in children. Skin-prick testing for common aeroallergens will identify the atopic preschooler. Sensitisation does not mean clinical allergy and a positive result should be correlated with the patient's clinical history. This will allow tailored and practical aeroallergen avoidance or eradication strategies and not 'blanket' avoidance advice. The latter is often too complicated for the patient to adhere to and will in most instances be unsustainable.

Peak flow-meter (PEFR) monitoring is useful in asthmatics over five years of age, especially in those children with severe or difficult-to-control symptoms. The PEFR is also a handy tool for evaluating a patient's readiness for discharge from hospital after an acute exacerbation; it forms a vital part of any asthmatic's self-management asthma treatment plan at home.^{5,20,22} The Asthma Action Plan incorporates peak-flow measurement in monitoring daily asthma symptoms, and different patient 'actions' are based on peak-flow measurements in the 'green (GO)', 'orange (CAUTION)' or 'red (STOP)' zones.²³ (These

action plans can be downloaded from the Allergy Foundation of South Africa's website at www.allergyfoundation.co.za.)

DIFFERENTIAL DIAGNOSIS OF ASTHMA IN CHILDHOOD

All that wheezes is not asthma. It is important to keep the 'mimics' of asthma in mind. The astute clinician will always ask the question: 'Is this really asthma?' A follow-up date should be arranged after starting inhaled corticosteroids, and if symptoms do not improve (despite excellent adherence and inhaler technique), the child should be investigated for other causes of persistent coughing or wheezing.^{5,20}

Post-infectious bronchiolitis obliterans (after infection by adenovirus and other respiratory viruses) is a chronic inflammatory disease of the medium and smaller airways and it is postulated to be underdiagnosed in children. This condition mimics asthma and causes ongoing symptoms of coughing and wheezing for longer than two months after an acute lower-airway infection. It can lead to bronchiectasis and severe impairment of quality of life.^{24,25}

Protracted bacterial bronchitis, according to the ERS, is diagnosed when all three of the following criteria are present: productive coughing (present for >4 weeks), the absence of other causes for the patient's symptoms and coughing that resolves with a 2- to 4-week course of appropriate oral antibiotics.²⁶ It is of utmost importance that lower-airway sputum cultures are obtained from these patients, especially after a poor response to a course of amoxicillin-clavulanic acid.²⁷

'Red flag' symptoms or signs indicate the need to investigate for the presence of an alternative diagnosis to asthma ('sinister wheezing' – see Figure 1). These symptoms include:

- the presence of respiratory symptoms from birth;
- progressive respiratory symptoms (instead of normal episodes in between);
- faltering growth
- digital clubbing
- no response to inhaled corticosteroids after three months of treatment, and
- focal (segmental) lung signs.

Asthma may co-exist with bronchiectasis and it is still not clear whether asthma is a cause of bronchiectasis or vice versa.²⁸ Referral to a pulmonologist or further investigations (see Table II) may be necessary if an alternative diagnosis is suspected.

POSSIBLE INVESTIGATIONS IN THE PATIENT WITH ONGOING ASTHMA SYMPTOMS WHO DOES NOT RESPOND TO INHALED CORTICOSTEROIDS (TABLE II).^{5,29–32}

TABLE II: SPECIAL INVESTIGATIONS TO RULE OUT 'MIMICS' OF ASTHMA

INVESTIGATION	COMMENTS AND INDICATED SITUATIONS
Nasopharyngeal viral aspirates to perform PCR or viral cultures	History of recurrent or prolonged wheezing and tachypnoea after viral respiratory infections. Prolonged oxygen requirement for hypoxia in suspected adenovirus infection (may indicate bronchiolitis obliterans).
Milk scan or contrast swallow	Respiratory symptoms while feeding and to rule out possible 'silent' reflux.
Chest X-ray (posterior-anterior and lateral views)	Indicated if unilateral, focal or monophonic wheezing is present. Indicated when asymmetrical chest signs are found on examination. A history of premature birth with prolonged oxygen administration may indicate bronchopulmonary dysplasia.
Sweat test	Suspect cystic fibrosis (CF) in a child with a family history of respiratory symptoms. Chronic coughing with growth faltering or additional gastrointestinal complaints (diarrhoea, fatty/bulky stools or severe constipation) may also indicate CF.
Primary or secondary immune deficiency work-up include: HIV and TB work-up, full blood and differential count, immunoglobulins (IgG, IgE, IgA and IgM). Confirm that vaccinations are up to date, then proceed to IgG levels to specific organisms (eg <i>Streptococcus pneumoniae</i>). ³³	Exclude secondary immune deficiency first. The history of recurrent infections, frequent hospitalisations requiring intravenous antibiotics or repeated/ prolonged courses of oral antibiotics to clear up infections may indicate a primary immune deficiency. Measure post-vaccination responses (IgG) if baseline antibody titres are below protective levels – a fourfold increase in titres after vaccination is considered adequate.
Nasal/airway ciliary biopsy and/or primary ciliary dyskinesia (PCD) gene panel	The presence of chronic suppurative otitis media, recurrent sinusitis or dextrocardia on chest X-ray may indicate primary ciliary dyskinesia.
High-resolution chest CT scan and/or bronchoscopy	Indicated if digital clubbing is present or bronchiectasis is suspected. These should be done to exclude congenital airway abnormality.
Cardiac ultrasound	Indicated if a cardiac murmur is present or the young child becomes exhausted during feeding.

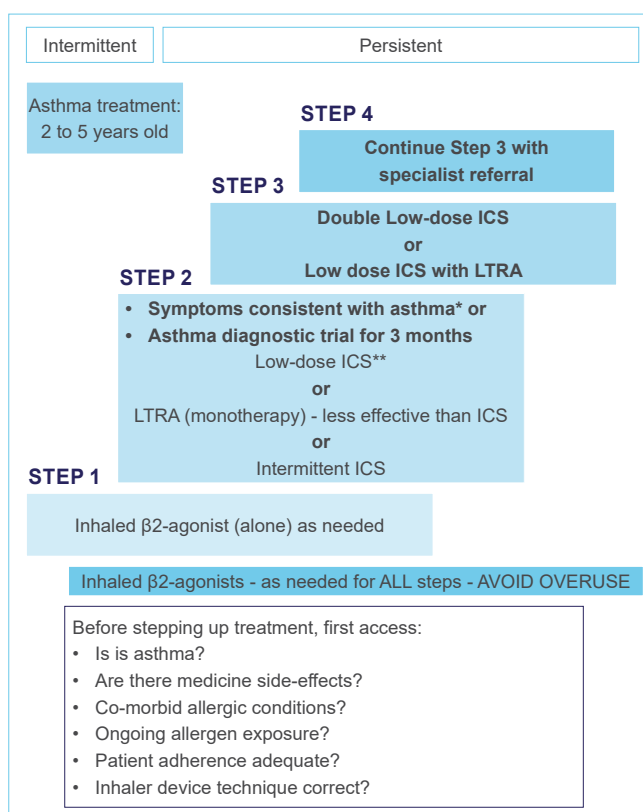


Figure 2: A stepwise approach to treating preschool asthma (adapted from the GINA guidelines).

*Symptoms consistent with asthma include: three or more symptom episodes per year or symptoms occurring every 6 to 8 weeks.

**Low-dose inhaled corticosteroids: budesonide 200 microgram/day or ciclesonide 160 microgram/day. ICS: inhaled corticosteroids. LTRA: leukotriene receptor antagonist (montelukast).

INITIATING ASTHMA TREATMENT: IS THERE STILL A PLACE FOR 'STEP 1' IN TREATING PRESCHOOL ASTHMA?

As mentioned previously, any initiation of inhaled corticosteroid therapy should be considered as part of a 'trial' treatment and its efficacy should be reviewed ideally in three months (Step 2 – GINA guidelines) – see Figure 2.²⁰ It should be stopped after three months, and if symptoms recur after treatment has ceased, the diagnosis of asthma has been made.

A major change in the GINA (2019) guidelines was recently published on the GINA website (available at www.ginasthma.org/reports). Short-acting β_2 -agonists (SABA) *alone* (Step 1) is no longer recommended for the treatment of asthma in adolescents and adults. Whether these recommendations will be translated into the management of preschool asthma, remains to be seen. SABA-alone does not treat the underlying airway inflammation, and the overuse of SABA has been shown to lead to β -receptor downregulation, decreased bronchoprotection, rebound airway hyperresponsiveness and a decrease in bronchodilator response over time. The overuse of SABA is also associated with a higher risk of emergency department presentations and even asthma-related deaths. No patient treated for asthma should be on an SABA alone.

PRESCHOOL ASTHMA TREATMENT: PRACTICAL RECOMMENDATIONS

Treating the preschool asthmatic offers many challenges and pitfalls. Based on the author's experience, adhering to the following basic principles may improve preschool asthma outcomes:

1. **Invest time in the preschool asthmatic.** Busy consulting rooms and tight schedules are major burdens in caring optimally for asthmatics. Consultation times should be prolonged, allowing enough time for asthma education. Education can be improved by providing patients with a written asthma action plan and an asthma diary. Make use of a translator, 'dummy' devices and a dedicated asthma nurse. Also make use of downloadable material from the Allergy Foundation of South Africa's website (www.allergyfoundation.co.za). Use videos (available on YouTube®) for practical demonstrations of the use of inhaler devices.
2. **Correct inhaler technique is of utmost importance.** Appreciate the fact that even with an excellent spacer technique, less than 10% to up to 15% of the active inhaled molecule is deposited into medium and smaller airways. If commercial spacers are not available at your institution, remember that 500 mL plastic bottles are excellent spacer devices (see Picture 1).³⁴ A spacer with a face mask should be used with children under four years of age and a spacer *without* a face mask should be used with older children.



Picture 1: 500 mL plastic bottles are excellent and cheap spacer devices (picture taken with the mother's consent).

3. **Take it one step at a time.** Parents are often bombarded with information and may feel overwhelmed, especially during the first consultation. The diagnosis of asthma can be quite intimidating. Conveying information to asthmatic patients should be an empathetic and ongoing process, with additional information added on to previous knowledge

during each subsequent consultation. Praise the asthmatic if previous mistakes were corrected – do not focus only on negative aspects.

4. **Upskill yourself.** Generally, healthcare practitioners show an enormous lack of knowledge when it comes to teaching patients the correct inhaler technique.³⁵ Upskill yourself by doing the National Asthma Education Programme (NAEP) – www.asthmasa.org.
5. **Treat AR (as a comorbid condition and a possible cause of poor asthma control) and eczema (to prevent ongoing and new allergen sensitisation) aggressively.**
6. **The safety and efficacy of long-acting beta2-agonists (LABA's) have not been established in children under four years of age.**³⁶ Monotherapy inhaled corticosteroids are the mainstay of treatment in this age group.
7. **Home nebulisers are not optimal.** Rescue treatment with SABA, delivered at the right dose and via a spacer, gives better lung deposition than home nebulisation. Home nebulisers do not run on oxygen and concerns about organism contamination should prompt the clinician to seldom, if ever, recommend the use of home nebulisers.
8. **Effectively deal with non-adherence. Poor adherence can be either deliberate or non-deliberate, and probably the biggest reason for asthma treatment failure.** The GINA and NAEP guidelines provide in-depth information on dealing with this.
9. **Follow up frequently – preferably by the same healthcare professional. No improvement means it is time to revise the diagnosis.** Most true preschool asthmatics would and should get better with a well-adhered-to inhaled corticosteroid treatment regime. If they do not, it might not be asthma.
10. **Cigarette smoking during pregnancy and exposure during childhood substantially hamper asthma symptom control.** Decreased pulmonary function is already demonstrable in infants whose mother smokes during pregnancy (even if these infants were not exposed to cigarette smoking after birth).³⁷
11. **Get caregivers on board.** Children spend most of their day under the supervision of caregivers and teachers. Caregivers and teachers should be taught how to interpret the asthma action plan and administer medicine in emergency situations. Environmental exposures at school (eg air pollution in busy suburbs, cockroaches and house-dust mite) should be kept in mind.³¹ Teachers should learn that every child with asthma should participate in sport – asthma is *not* a contra-indication for performing physical activity and exercise.

PROGNOSIS OF PRESCHOOL ASTHMA

According to the World Allergy Organisation (WAO), about half of all preschool wheezers will be completely asymptomatic by school age, irrespective of treatment. In a cross-sectional study in France, mild and episodic viral-induced wheezing carried an excellent prognosis of being symptom-free at five years of age. Other prospective studies have so far failed to predict accurately the chance of outgrowing asthma. Children with atopy seem to continue to wheeze beyond five years of age.³⁸ The severity,

frequency and intensity of wheezing (emergency visits, requiring hospital admissions) in early childhood seem to be the most sensitive indicator of protracted wheezing and asthma later in life.¹⁷

Unfortunately, the only answer to the question 'Is my child going to outgrow asthma?' is simply this: 'We don't know!' A careful 'wait-and-see' strategy is the most scientific answer we can currently offer our patients.

CONCLUSIONS

South Africa's statistics on asthma are worrisome. With only a

handful of medications at our disposal to treat preschool asthma, it is time that primary healthcare practitioners and paediatricians get the basics right. This can happen only when asthma carers upskill themselves, spend more time on educating their patients about asthma, follow up the preschool asthmatic more closely and deal effectively with non-adherence.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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