Asthma in young children

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Highlights / Hoogtepunte

- Understand the pathophysiology and causes of wheezing in children, and make a better and quicker asthma diagnosis.
- A practical and stepwise approach to the management of chronic asthma in young children.
- Can childhood asthma be outgrown? Is bone growth significantly reduced with inhaled corticosteroids? Should children with chronic chest complaints be treated with regular courses of antibiotics?
- Verstaan die patofisiologie en oorsake van 'n fluitbors in kinders, en maak 'n beter en vroeër diagnose van brongiale asma.
- 'n Praktiese en stapsgewyse benadering tot die hantering van asma in jong kinders.
- Kan kinderasma ontgroei word? Onderdruk inhalasiesteroïede beengroei betekenisvol op lange duur? Moet kinders met chroniese longklagtes met gereelde kursusse antibiotika behandel word?

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1. INTRODUCTION

Transient wheezing in infancy is more likely to be a function of small airways, and wheezing in the first year of life does not persist as asthma in two-thirds of those afflicted. The bottom line, however, is that no infant or child should be treated with regular courses of antibiotics for chronic chest symptoms, as is currently the vogue. A second misconception is that real asthma in childhood is frequently outgrown. This is not the case: on average only about one third of patients have some symptom relief at the time of puberty. The principles of treatment of young asthmatic children are the same as in the older child and adult. However, there are some special situations, which are discussed in the article.

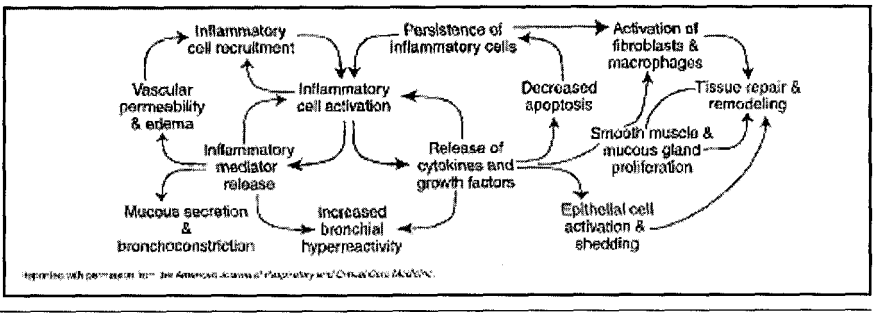
2. PATHOPHYSIOLOGY

Asthma may develop at any age. The younger the child, however, the more difficult the diagnosis and treatment. Even the definition of the disease is more complex in this age-group. The broad outline of the definition employed by the Global Initiative for Asthma (GINA), namely that "*asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway reactivity that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.*"[1] still applies but, since the diagnosis rests almost entirely on clinical parameters, special care needs to be taken to exclude other diagnoses.

There is no question that in true asthma the process of chronic inflammation is well established, even in young children and mild cases.[2,3] Today, this process is more important than ever, since it is intimately connected with the processes of tissue repair and remodelling **(figure 1).**[4] Hence, the young child who wheezes and coughs is critically balanced between two narrow extremes of over-treatment and under-treatment. For most asthmatics the process has begun before going to school,[1] and childhood asthma is closely linked to the development of atopy,[5] rather than small airway calibre.

Transient wheezing in infancy is more likely to be a function of small airways,[6] and wheezing in the first year of life does not persist as asthma in two-thirds of those afflicted.[7] The close relationship between atopy and viruses is such that atopy probably predisposes to a **sensitivity of the airway to viruses,** which are the most important triggers of acute exacerbations of asthma in younger children and infants.[8] There are, however, not more infections, but infections are more severe. The wheezy infant is thus usually not asthmatic and the pathophysiology of this condition is not one of inflammation but rather of anatomically small airways.

Figure 1: Mechanisms of acute and chronic inflammation in asthma and remodelling[1]



However, it is important to remember that true asthma with inflammation occurs at any age, including infancy.

3. THE AETIOLOGY OF ATOPY

There is a clear association of genetic influence and origin of asthma and atopy, although the exact genetic loci are still being determined. Of particular interest to the epidemiological trend of rising prevalence of allergic diseases is the so-called "Hygiene Hypothesis." There are indications that improvements in hygiene, together with reduction in rates of respiratory infections in infancy, are strongly associated with increasing prevalence of atopic diseases in Western countries.[1] The mechanism of this finding is through influence on the Th_1/Th_2 cellular pathways of the immune system. Interferon gamma (IFN-γ) drives Th_1 development away from the Th_2 or atopic pathway. Greater exposure to bacteria or bacterial products during early life increases IFN-γ, which is normally present in lower circulating levels in atopic infants. It can be postulated that the artificial reduction in bacterial exposure, through improvements in public health and hygiene, changes in infant diets, early use of antibiotics and smaller family size, contributes to a reduction in IFN-γ.[9]

4. THE PROGRESSION OF THE DISEASE

The usual presentation of asthma in infancy is wheezing but since not all wheezing in this age group is asthma, care should be taken with a differential diagnosis. **(Table 1)** The first episode of wheezing in this group of patients is likely to be labelled "bronchiolitis", a specific acute inflammatory disease of the bronchi caused by the Respiratory Syncitial Virus (RSV) and, much less commonly, other viruses.[10] **(Table 2)** This condition is short-lived, associated with a mild upper respiratory tract infection, low-grade fever and hyperinflation of the chest and may be quite profound. RSV infection can predispose to asthma, but this may be due to a pre-existing immune disorder predisposing to allergy and infection.[1]

Recurrent wheezing in infancy may be atopy-associated asthma or small-airway disease. The latter category is more likely but again the disease has important quality of life issues and may be quite severe, hence a trial of anti-asthma therapy is usually indicated. A chronic cough in a young child will create the same diagnostic dilemma, and again a differential diagnosis is important **(Table 3)**, especially in the child who is failing to thrive, has a cardiac murmur or vomits regularly. The bottom line, however, is that no infant or child should be treated with regular courses of antibiotics for chronic chest symptoms as is currently the vogue.[11] In addition to being a complete waste of time (as almost all respiratory tract infections in childhood are viral in aetiology), their abuse may be contributing to the rising prevalence of allergic diseases (see the hygiene hypothesis) and to increasing drug resistance.

A further misconception is that asthma in childhood is frequently outgrown. This is, however, not the case and on average only about one third of patients have some symptom relief at the time of puberty.[12] Many of these children, however, develop symptoms again in later life.[13,14] For this reason it may be possible, and even essential, to reduce or stop therapy in adolescence, but the patient and his/her parents should be alerted to the possibility of recurring symptoms. This point is especially important since the patient frequently changes his asthma doctor at this age; continuity of care is necessary to avoid delays in time and costly diagnostic procedures.

Asthma is more common in boys in childhood, probably related to smaller airways and greater frequency of atopy in males at this age.[15-18] Although quality of life and socio-economic factors are difficult to quantify in young children, this is an age group when recurrent illness and decreased activity will have a profound impact on development and socialisation of the child. In a study conducted in the Nordic countries,

Table 1: Causes of persistent wheezing in young children

- Asthma
- Small airways
- Aspiration syndromes
- Cystic fibrosis
- Bronchiectasis
- Bronchopulmonary dysplasia
- Foreign body
- Enlarged lymph nodes
  - Tuberculosis
  - HIV
- Mediastinal tumour
- Congenital anatomical disorders
  - Tracheo-bronchomalacia
  - Vascular ring
  - Cysts
  - Lobar emphysema

Table 2: Respiratory viruses and respiratory conditions associated with them[1]

Virus type	Serotypes	Common Cold	Asthma exacerbation	Pneumonia	Bronchitis	Bronchiolitis
Rhinovirus	1-100 (plus)	+++	+++		+	+
Coronavirus	229E and OC43	++	++	-	-	-
Influenza	A, B, and C	+	+	++	+	
Parainfluenza	1, 2, 3, and 4	+	+		++ (laryngotracheo-bronchitis)	+
Respiratory	A and B	+	+	+	+	+++
Adenovirus	1-43	+	+	++	+	+

Table 3. Differential diagnosis of a chronic cough by nutritional status

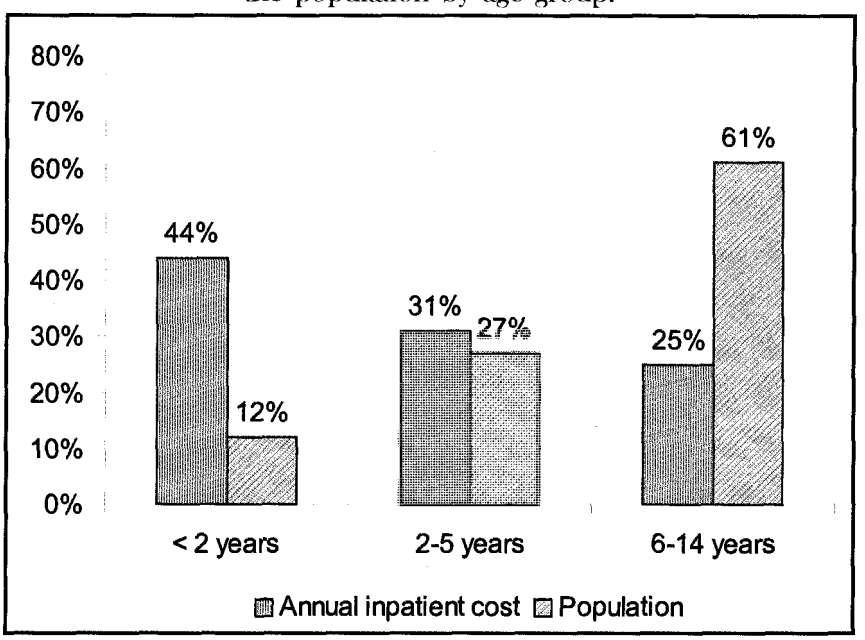
Nutritional status	Clinical pointer	Probable cause
NORMAL	• Exercise, nocturnal symptoms with/without wheeze • Upper airway symptoms • Whoop • Right middle lobe (RML) syndrome	• Asthma • Post nasal drip • Chronic sinusitis • Non-infectious rhinitis • Pertussis-like syndrome • Foreign body
VARIABLE ANTHROPOMETRIC MEASUREMENTS	• Vomiting (GORD, in co-ordination with swallowing and trachea-oesophageal fistula) • Recurrent respiratory and other systemic illnesses • GI signs (abnormal stools) • Prolonged oxygen exposure • Cardiac signs	• Aspiration syndromes • Immune deficiency • Cystic fibrosis • Broncho-pulmonary dysplasia (BPD) • Cardiac pathology • Cardiac failure
FAILURE TO THRIVE	• Lower socio-economic circumstances • Chronic diarrhoea, candida • Lymphadenopathy • Productive cough, abnormal stools • Progressive dyspnoea	• Tuberculosis • HIV infection • Cystic fibrosis (Bronchiectasis) • Interstitial lung disease

children less than 2 years of age accounted for 44% of annual inpatient asthma costs and children 2-5 years old for 31% of such costs, even though the former group made up only 1% of the asthma population and the latter group 27%.[19] **(Figure 2)**

5. DIAGNOSING ASTHMA IN CHILDREN

In chronic asthma, a definite diagnosis may be difficult to obtain in young and older children. If the diagnosis is unclear, specialist assistance should be sought. Asthma should be suspected in any child with wheezing (ideally heard by a health care professional on auscultation and distinguished from upper airway noises), dry cough, breathlessness and noisy breathing. A detailed history and physical examination is mandatory, and the physician should pay specific attention to the pattern of disease, severity and control, and differential clues. In schoolchildren, bronchodilator responsiveness and PEF variability may be used to confirm the diagnosis. Although allergy is not essential in the diagnosis of asthma, allergy tests may be helpful in seeking causal factors and making the diagnosis of atopy. The absence of allergy in a schoolchild with symptoms suggestive of asthma should prompt consideration of another diagnosis.

Figure 2: Percentage of 1999 inpatient costs vs. proportion of the population by age group.



Indications for specialist referral are the following[20]:

- Whenever the diagnosis is unclear or in doubt.
- Symptoms present from birth, or perinatal lung problems.
- Excessive vomiting or posseting.
- Severe upper respiratory tract infection.
- Persistent wet cough.
- Family history of unusual chest disease.
- Failure to thrive.
- Unexpected clinical findings (e.g. focal signs in the chest, abnormal voice or cry, dysphagia, inspiratory stridor.)
- Failure to respond to conventional treatment (Particularly to inhaled corticosteroid therapy above 400mcg per day or frequent use of oral steroid therapy.)
- Parental anxiety or need for reassurance.

6. MANAGEMENT

a. Prevention of Asthma

Prevention of asthma has been the life-long goal of many allergists. However, progress in this regard has, to date, been very disappointing from a practical point of view. A number of exciting strategies for prevention are being investigated[21], but need further research.

Primary prevention:

Attempts to provide allergen-free diets to pregnant mothers have failed to prevent the development of allergy and asthma.[22] Aero-allergen avoidance is unhelpful and may even promote atopy[23], and even allergen avoidance in breast-feeding mothers (foods) to high-risk infants (aero-allergens) is unhelpful and even detrimental.[24,25] Even cigarette exposure is not conclusively linked to asthma aetiology, although it is a major factor in wheezy infants and a cause of asthma exacerbations.[26,27] As yet there is no practical advice that can be given to the parents of soon to be or newly born high-risk infants.

Secondary prevention:

The administration of newer anti-histamines to clearly atopic infants with eczema has, likewise, been disappointing in the overall prevention of asthma.[27,28] The ETAC-Study found that only a subset of atopic infants had a reduced prevalence of wheeze after receiving Cetirizine. Specific immuno-therapy shows promise[29], but is clearly impractical unless orally available. Again no practical advice can be given.

Tertiary prevention:

The avoidance of allergens and irritants in the established asthmatic are important adjuncts to treatment and prevention of acute exacerbations. Acute exacerbations of asthma, together with uncontrolled symptoms, are the main cost drivers in this disease[30] and certainly impact significantly on the quality of life of the patient. It should be stated that the successful treatment of allergic rhinitis will improve the outcome of asthma.[31]

b. Treatment of the young asthmatic

The literature is full of algorithms for the management of both chronic and acute asthma in children,[32-36] but treatment of the pre-school (younger than 5 years) child is seldom stressed. The principles of treatment of young asthmatic children (5-12 years) are the same as in the older child (>12 years) and adult. In **Figure 3 (page 60),** different tables of the GINA report have been condensed into a reference guide. The level of severity should first be determined before commencing with any treatment. To gain initial control, there are two approaches. First, one can gain control with a higher level of therapy than the level of severity, and then step down. Secondly, one can gain control by starting at the level of severity and step up to a higher level of therapy. The first approach is often preferred.

It should be noted that the **daily controller medications** are the first line options for the initial treatment. Only if inhaled corticosteroids are contra-indicated, if the first line combinations fail to control symptoms or if special asthma conditions exist should other treatment options be considered.

The recommended daily dosages of inhaled corticosteroids, according to the South African Collaborative Asthma Working Group (SACAWG), are depicted in **table 4**. The correct paediatric dose of other medications should at all times be confirmed by consulting a formulary.

A trial of other add-on therapy should be carried out before increasing the inhaled steroid dose to >400mcg per day (or >200mcg in the higher mcg potencies drugs).

The appropriate inhaler device should at all times be selected. In general, the following guidelines apply:

- **Children younger than 3 years**: **pressurised MDI** (pMDI) plus a **spacer with a face mask**, or, if necessary, a nebuliser with a face mask
- **Children older than 3 years**: **pMDI** plus **spacer with a mouth-piece**, or a dry powder inhaler (DPI), or, if necessary, a nebuliser with a face mask
- **Children of any age over the age of 6 years** who have difficulty using a pMDI, should use a pMDI with a spacer, a breath-actuated inhaler, a DPI or a nebuliser. DPI's require an inspiratory effort that may be difficult to achieve during severe attacks.
- **Children who are having severe attacks** should use a pMDI with a spacer or nebuliser.

c. Drugs in asthma control

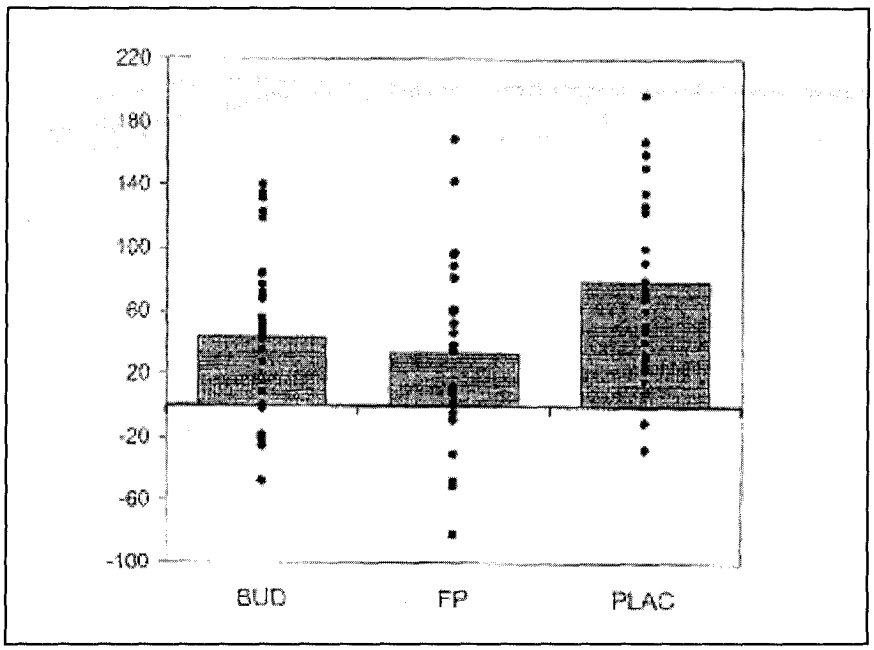
Inhaled cortico-steroids:

These drugs remain the mainstay of treatment and their use has become standard. Despite concern over safety in young children and even evidence of short-term effect on growth[37] **(Figure 4)**, this is not evident in long-term studies.[38,39] The use of Budesonide[39] and Fluticasone[40,41] is especially advantageous in this population. However, their routine usage may not be cost-effective over that of beclomethasone at doses of less than 400ug daily, where side effects are extremely unlikely.[41] Children and even infants with more persistent wheeze should be given a trial of inhaled corticosteroids as this is the only treatment modality that may relieve symptoms and improve quality of life.[43-45] Although there is no sound scientific proof that oral and inhaled steroids do improve the outcome of bronchiolitis,[46,47] they may be tried as adjunctive therapy in the hospitalised infant. The choice of inhaler device is critically important for children and the preferred device for children younger than 4 years

Table 4: Recommended daily dosages of inhaled corticosteroids. (All dosages are in micrograms)

Drug	Low dose	Medium dose	High dose
CFC beclomethasone	100-200	200-400	>400
Budesonide MDI	100-200	200-400	>400
Triamcinolone	100-200	200-400	>400
Budesonide turbohaler	100	100-200	>200
HFA beclomethasone	50-100	100-200	>200
Fluticasone	50-100	100-200	>200

Figure 4: Mean (lines) and individual (circles) short-term lower-leg growth rates (in mm/year) during treatment with Budesonide (BUD), Fluticasone proprionate (FP), and Placebo.



is a dedicated face-mask spacer (with one-way valve) with a metered-dose inhaler.[1] Nebulisation is an alternative, but this is a cost-inefficient delivery system. Powder devices may be used in children over 6 years of age.

Long-acting β_2 agonists:
A new classification of β_2 agonists exists **(Figure 5)**. Duration of action is not the only difference between formoterol and aalmeterol. Formoterol's mechanism of action also allows dose increase with exacerbations.[48] The value of these drugs in older children is controversial, because they have not shown the same efficacy as in adults.[49,50]

In young children (2-5 years) there is no information whatsoever and their use is extrapolated from data for school-aged children and even adults. Anecdotal clinical experience suggests that there is a place for their use, but only once the dose of inhaled steroid is significant, the diagnosis of asthma is established and symptoms persist.

The need for frequent use of beta-2 agonists generally indicates a significant inflammatory process that should be controlled with anti-inflammatory drugs.[51-53] Inhaled corticosteroids are currently the most effective anti-inflammatory drugs used for long-term control of asthma. The use of long-acting beta-2 agonists as monotherapy appears worse than inhaled corticosteroid therapy.[54] Long-acting beta agonists are not steroid sparing, but may in actual fact be inflammation-masking, albeit short term improvement of symptoms. Therefore, most asthma consensus statements[55-58] recommend the use of long-acting beta-2 agonists only in addition to inhaled corticosteroids. The addition of these agents may be considered when asthma control is unsatisfactory despite moderate to large doses of inhaled corticosteroids, or when the dose of corticosteroid required to achieve control of symptoms is associated with significant side effects.

They do, however, improve nighttime and daytime symptoms and quality of sleep, reduce the requirement of short-acting beta 2 agonists and protect against; metacholine, cold air-induced and exercise-induced bronchoconstriction.[51,59,60] They are considered the first choice add-on therapy to inhaled steroids in children (5-12 years).

The most cost-effective approach is, nevertheless, the initial trial of inhaled corticosteroids, irrespective of the severity of the disease, followed by add-on therapy only with breakthrough exercise or nocturnal symptoms. Another important point that is not often stressed is that the initiation of chronic asthma maintenance therapy must only be commenced when the patient is free of regular symptoms.

This implies that a patient with ongoing daily symptoms must first be treated for acute asthma with either an oral steroid or increased dosage of inhaled therapy (rapid-acting inhaled β_2 agonist plus inhaled corticosteroid). Failure to do this is to invite tail-chasing with regard to medicines.

Leukotriene antagonists:
These agents are orally available, safe and efficacious in children from 2 years and older. They are not as effective as inhaled corticosteroids for first line therapy and should not be prescribed as alternatives to inhaled corticosteroids in young children with mild persistent asthma. They do however, provide an alternative to long-acting B_2 agonists as add on therapy. As there is no evidence yet for their disease modifying benefit, they remain second line drugs in this indication.

Therapies with limited efficacy, excessive cost, and/or unacceptable side-effects:
Sodium cromoglycate, anti-histamines, oral theophyllines, Specific Immunotherapy and ketotifen all are unsuitable therapies for young children, either

Table 5: Onset and duration of action of inhaled β_2-agonists[1]

Onset of Action	Duration of Action	
	Short	Long
Rapid	Fenoterol Pirbuterol Procaterol Salbutamol (Albuterol) Terbutaline	Formoterol
Slow		Salmeterol

because of very limited efficacy (sodium cromoglycate, anti-histamines and ketotifen), excessive cost (sodium cromoglycate) or unacceptable side-effects (theophyllines and SIT). **Their use cannot be justified under any circumstances.** In addition the value of alternative and complementary therapies, such as homeopathy, acupuncture, herbal medicine and chiropractic manipulation are either not researched or lacking in efficacy.[62,63] These therapies are NOT NATURAL and carry risks.

CONCLUSION

In summary, it is obvious that the pre-school or young child is not just a smaller version of the older child or adult. This is especially true of asthma therapy, where special situations exist with regard to diagnosis and treatment. Rational selection of therapy must at all times be based on sound evidence. Only in the absence of this should clinical judgement and anecdotal experience suffice.❐

Please refer to the CPD questionnaire on page 53.

Acknowledgement

Figure 3 (page 60) has been compiled using figure 8, 9 and 10 and sections of part 4 of the document. No changes were made to the original source. We greatly acknowledge the source and do recommend that readers refer to the source for additional information. The complete GINA-report of 2002 is available at *www.ginasthma.com*

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